PB80-213937

Trifluralin (Treflan)
Position 1/2/3

(U.S.) Environmental Protection Agency
Arlington, VA

22 Aug 79

U.S. Department of Commerce
National Technical Information Service
NTIS

PB80-213937

EPA/SPRD-80/21

TRIFLURALIN (TREFLAN) POSITION DOCUMENT 1/2/3

Special Pesticide Review Division
Office of Pesticide Programs

AUG 22 1979

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U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

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50272-101

REPORT DOCUMENTATION PAGE

1. REPORT NO. EPA/SPRD-80/21

2.

3. Recipient's Accession No. PB 80 213937

4. Title and Subtitle
Trifluralin (Treflan): Position Document 1/2/3

5. Report Date 8/22/79

6.

7. Author(s)

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
Special Pesticide Review Division
Environmental Protection Agency
Crystal Mall #2
Arlington, VA

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address
Environmental Protection Agency
401 M St S.W.
Washington, D.C. 20460

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Preliminary Risk Assessment: Examination of possible unreasonable risks associated with uses of pesticide and a gathering of all available information to determine whether or not this or any other risk does exist. Initiates literature search and evaluates risk data. Limited information on exposure to forecast extent of risk.

Risk/benefit analysis: qualitative & quantitative risks of a pesiticde, value of crop uses, availability of alternative pesticide, exposure to man and environment. Identification of risk reducing regulatory options and proposed Agency action.

17. Document Analysis a. Descriptors
0703,0605,0504

b. Identifiers/Open-Ended Terms
0606

c. COSATI Field/Group

18. Availability Statement:
Release Unlimited

19. Security Class (This Report) Unclassified

20. Security Class (This Page) Unclassified

21. No. of Pages

22. Price

(See ANSI-Z39.18) See Instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

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I. Introduction

A. Regulatory History

On February 3, 1977, Congressman Andrew Maguire, Congressman Henry Waxman, the Migrant Legal Action Program (MLAP), the Maricopa County Legal Aid Society, and several migrant farmworkers petitioned the Agency to suspend the registrations of Treflan (EPA Reg. No. 1471-35), Trysben 200 (EPA Reg. No. 352-250), and Benzac 1281 (EPA Reg. No. 264-92), under Section 6(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)(7 U.S.C. 136 *et seq.*), because carcinogenic nitrosamines had been found to contaminate them (Fine et al., 1976).[1/]

The petitioners claimed:

> The continued use of nitrosamine-containing herbicides will have an unreasonable adverse effect on the environment and constitutes an imminent hazard to man during the time required for cancellation. The risks involved in the case of Trysben 200, Benzac, and Treflan far outweigh their benefits when viewed in light of the fact that: (a) these three herbicides have been found to contain significant quantities of nitrosamines; (b) nitrosamines are known to be potent carcinogens; and (c) there is a high risk of human exposure to these herbicides in agricultural and garden use (42 FR 10886, February 24, 1977).

[1/] The Agency subsequently agreed to the registrants' requests to voluntarily cancel the Trysben 200 and Benzac 1281 registrations. 43 FR 5567, February 9, 1978; 43 FR 35099, August 8, 1978.

In preparing its response to the petition, the Agency sought information at a hearing held pursuant to FIFRA Section 21(b) in Phoenix, Arizona on March 7, 1977 and in Washington, D.C. on March 9, 1977 (42 FR 10886, February 24, 1977). This hearing was attended by a number of Congressmen, farmers, the MLAP, farm workers, grower association representatives, the Treflan registrant, and university researchers who provided both oral and written information relevant to this issue. Hearing transcripts and written comments made for the record at this hearing are available for inspection in the Office of the Federal Register Section, Room EB-47, East Tower, 401 M St. S.W., Washington D.C. 20460. Additional data were also obtained from the U.S. Department of Agriculture (USDA), other Federal agencies, and a number of individuals. These data are also available for inspection.

On the basis of this information, the Agency decided not to suspend the Treflan registrations (42 FR 40009, August 8, 1977). The Agency determined that continued Treflan use would not constitute an "imminent hazard" as defined under § 6(c)(1) of FIFRA since the risks associated with that use during the period necessary to pursue cancellation proceedings were substantially exceeded by the benefits.

However, the Agency also concluded that the Treflan nitrosamine contaminant (N-nitroso-di-n-propylamine, NDPA) met or exceeded the oncogenic risk criterion,[2] and that, therefore, an RPAR should be issued. The Agency also indicated that it would investigate the possibility that NDPA-contaminated Treflan met or exceeded other additional risk criteria.

In September 1977, as part of its RPAR investigation and as required by the August 1977 Response to the Suspension Petition, the Agency met with the Treflan registrant and established test protocols to assess NDPA exposure to applicators, incorporators, mixers, loaders, and field workers. The registrant performed these studies and submitted the results in March 1978 (Day et al., 1978). These data, other information from the literature, and information on uses of Treflan and general agricultural practices for Treflan-treated crops, provided at a meeting of the Agency, USDA, and the registrant in Indianapolis, Indiana (June 20-23, 1978), were used to calculate worker exposure to NDPA due to Treflan use.

2/ 40 CFR §162.11(a)(3)(ii)(A) provides that if any ingredient of a pesticide has been found to induce oncogenic effects in experimental mammalian species or man from oral, inhalation, or dermal exposure, an RPAR shall be issued against that pesticide. Initially, the Agency decided not to proceed against Treflan individually, but to initiate an RPAR action against all pesticides which contained NDPA. Subsequently, however, the Agency decided not to delay regulatory action regarding Treflan until the entire class of NPDA-containing pesticides had been identified and reviewed.

Because most of the trifluralin produced is formulated as Treflan EC,[3] the RPAR review focused primarily on the risks and benefits of Treflan use. The Agency's proposed regulatory actions pertain, however, to all trifluralin-containing pesticides.

The Agency's consideration of the risks associated with trifluralin use has been based upon risk and exposure data collected not only from the sources described above, but also through a worldwide literature search. During the collection and evaluation of risk information, the Agency also solicited and received benefits and use data from the USDA, the registrant, and scientists.

The Agency has now concluded its RPAR investigation of trifluralin. The procedures followed in the trifluralin RPAR differ somewhat from those usually followed in an RPAR review. Normally, when one or more of the Section 162.11 risk criteria has been met or exceeded, a position document (PD 1) is issued in which the registered pesticide is presumed against. The registrant and other interested persons are given the opportunity to submit rebuttal evdience against the presumption of risk as well as evidence regarding the economic, social, and environmental benefits of the pesticide's use. If one or more of the presumptions of risk is not rebutted, the Agency must determine whether the continued use of the pesticide would cause "unreasonable adverse effects on the environment" (Section 6(b) FIFRA). Section 2 (bb) of FIFRA defines "unreasonable adverse effects on the environment" to mean "any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of use of any pesticide." Therefore, if the risks of a pesticide's use outweigh the benefits, the Administrator must issue a notice of intent either to cancel or deny the pesticide's registration without qualification or to cancel or deny the pesticide's registration if the registrant fails to meet Agency requirements which would reduce risks to a level where they are exceeded by the benefits (Sections 6(b) and 3(c)(6) of FIFRA). The United States Department of Agriculture (Section 6(b) of FIFRA), the Scientific Advisory Panel (Section 25(d) of FIFRA), and the public[4/] review the Administrator's proposed notice of intent to cancel or deny. The Administrator then considers all the comments which were made in a timely manner before publishing a final decision.

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[3] Confidential data submitted to EPA by the single trifluralin producer during the USDA/EPA/State agricultural colleges/registrant meeting in Indianapolis, Indiana, June 1978.

[4/] Although not required by law, it has been Agency policy to initiate a public comment period upon referral of the Administrator's proposed notice of intent to cancel.

In the case of trifluralin, two of the analytical RPAR phases - the initial determination that the risk criteria had been exceeded and the weighing of risks and benefits to determine the appropriate regulatory action -- have been combined, uninterrupted by the rebuttal comment period. The Agency believes that this modification is justified by the unusual circumstances associated with the trifluralin review. Moreover, the approach used has not denied the public the opportunity to comment on any determinations or issues raised by this position document.

Regarding the special circumstances of this RPAR, a hearing was held to obtain information concerning whether or not EPA should suspend the Treflan registration. Such hearings are not usually part of the RPAR process. During this hearing, the primary U.S. trifluralin registrant presented its position concerning Treflan risk. It conceded that the N-nitroso-contaminant was carcinogenic, but it asserted that Treflan was still safe to use because, due to low exposure, the risk was slight, and the substantial benefits outweighed that slight risk.[5] To some extent, therefore, the primary trifluralin registrant has had an opportunity to rebut the presumption that NDPA-contaminated Treflan is an oncogen. In addition, the registrant and others have submitted detailed papers regarding many of the aspects of risks which have been considered by the Agency in making its determination. Furthermore, the Agency, with the aid of USDA and state agricultural colleges, considered benefits data presented by the registrant when its benefit determination was made.

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[5] Transcript of Public Hearings on Petition to Suspend Certain Pesticide Products Section 6, FIFRA. March 7, 1977, Phoenix, Arizona, p. 11-26 and March 9, 1977, Washington, D.C. p. 2-13 through 2-23.

Much of what the registrant would have submitted at the usual RPAR rebuttal stage, therefore, has already been submitted during the modified trifluralin RPAR. It seems reasonable, therefore, to focus public discussion on the risk/benefit analysis by presenting the Agency position in a single document followed by a public comment period during which time the registrant and anyone else may submit comments[6/] in response to the Agency's tentative risk/benefit conclusions regarding trifluralin. The Agency believes that neither the registrant nor any other interested person has been prejudiced by this procedural modification since they will not be deprived of their opportunity to participate meaningfully in the administrative decison-making process affecting the continued registration of this pesticide.

[6/] Under 40 CFR § 162.11(a)(1)(i), only a registrant has the right to submit rebuttal evidence when its registered pesticide has been presumed against. It is Agency policy, however to allow anyone to submit timely evidence and to consider such evidence before making regulatory decisions.

B. Chemical Background

1. Nomenclature

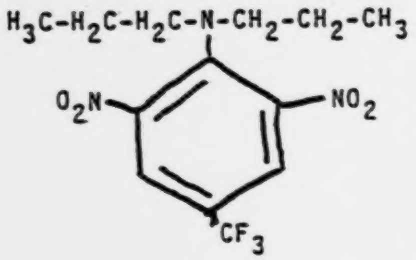
Trifluralin (CAS 1582-09-8), a pre-emergence herbicide, is the common name for the dinitroaniline compound alpha, alpha, alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine. This compound, first described by Alder et al. (1960), is also known as:

N, N-di-n-propyl-2,6-dinitro-4-trifluoromethylaniline;
4-(Di-n-propylamino)-3,5-dinitro-1-trifluoromethylbenzene;
2,6-dinitro-N,N-di-n-propyl-alpha-trifluoro-p-toluidine;
N,N-Dipropyl-4-trifluoromethyl-2,6-dinitroaniline; and
2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)-benzenamine

Trade names for formulated trifluralin are Elancolan, L-36352, Lilly 36,352, Su Seguro Carpidor, Trefanocide, Treficon, Treflan, Trifluoralin, Trifluraline, Triflurex, and Trim (Tracor-Jitco, 1977). The most commonly used trade name is Treflan.

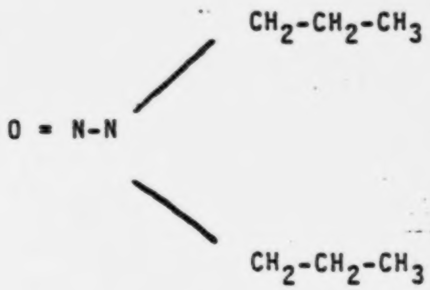
2. Chemical and Physical Characteristics

The molecular weight of trifluralin is 335.3; its molecular formula is $C_{13}H_{16}F_3N_3O_4$; and its chemical structure is:



Trifluralin, a yellow-orange crystalline solid, melts from 48.5° to $49.0^{\circ}C$, and boils from 96° to $97^{\circ}C$ at 0.18 mm Hg. Its vapor pressure is 1.99×10^{-4} mm Hg at $29.5^{\circ}C$. Some of its solubilities in grams per 100 ml at $27^{\circ}C$ are: acetone (40), ethanol (7), xylene (58), and water (less than 1 ppm) (Hilton, 1974).

Technical trifluralin is reported to be more than 95% pure (National Academy of Science, 1977). The impurity of concern, N-nitroso-di-n-propylamine (NDPA) is a symmetrical dialkylnitrosamine; its molecular formula is $C_6H_{14}N_2O$, and its chemical structure is:



The molecular weight of NDPA is 130.19, its density is 0.9163 at $20^{\circ}C$, and its boiling point is $78^{\circ}C$ at 8 mm Hg. NDPA's vapor pressure is 0.104 mm Hg at $26^{\circ}C$ (Probst, 1978). Nitrosamines are generally soluble in methanol, ethanol, acetone, and ether (Bontoyan, 1978). NDPA solubility in water is 7.6 mg/l (Monitoring Data Support Division, 1978).

It was first brought to the Agency's attention that Treflan, Trysben 200, and Benzac 1281 contained N-nitroso contaminants at an annual meeting of the American Chemical Society (Fine et al., 1976). At that meeting NDPA was identified at a level of 154 ppm in Treflan samples. Subsequently the Treflan registrant has decreased this level to less than 1.0 ppm by modifying the synthesis process. NPDA can be produced in trifluralin from the nitrosation of dipropylamine by residual nitrogen oxides in the reaction mixture during the latter part of product synthesis (Severn, 1977). In addition, NDPA may be a contaminant of the dipropylamine feedstock (Des Rosiers, 1978).

C. Uses and Production

1. Registrations and Use

Trifluralin has been registered for use on an increasing number of crops and ornamental plants since it was first registered in January, 1963. The 105 registered trifluralin products (56 Federal, 39 State, and 10 special local needs registrations) are formulated with trifluralin as the sole pesticidal active ingredient, in combination with other pesticidal active ingredients, with fertilizers, or with both.

These 105 registered products can be categorized thus: technical material (7), professional use on ornamentals/ nursery use (7), domestic use (37), and agricultural use (54). In addition to these, trifluralin is also registered as a tank mix with Eptam, Diphenamid, and Sencor. Trifluralin products formulated for use contain from 0.095% to 44.5% active ingredient.

The estimated use of trifluralin in 1972 by national region in millions of pounds was: Northeast, 0.4; Southeast, 2.3; North Central, 6.5; South Central, 6.2; Northwest and Southwest, 1.6. In addition, about four million pounds of trifluralin were exported in that year (von Rumker et al., 1974).

Section III of this document includes the estimated agricultural use of trifluralin by crop category.

Trifluralin is used once a year for pre-emergent control of annual grasses and some annual broadleaf weeds. It is normally applied before planting to field and vegetable crops such as soybeans and cotton. It is also applied to ornamental trees and shrubs, roses, certain established flowers, and fruit and nut trees after planting. The emulsifiable concentrate is the major formulation in use, but granular formulations are also used in smaller amounts.

Trifluralin is applied by low pressure surface sprays (20-40 psi), hand or machine broadcast, subsurface layering, and in a few instances, by air spraying. Soil incorporation within 24 hours is recommended for most trifluralin uses. For some products, surface application or surface application followed by irrigation is recommended. At the recommended application rates, from 0.25 to 4.0 pounds of active ingredient are applied per acre of soil surface.

2. Tolerances

Table 1 gives tolerances for trifluralin. There are no established tolerances for the NDPA contaminant of trifluralin in or on raw agricultural commodities, processed food, or feed.

3. Production

Section 7(c) of FIFRA requires producers to inform the Administrator of the types and amounts of pesticides and, if applicable, active ingredients used in producing pesticides in their establishments.

Section 7(d) of FIFRA specifies that:

> Any information submitted to the Administrator pursuant to Subsection (c) other than the names of the pesticides or active ingredients used in producing pesticides produced, sold, or distributed at an establishment shall be considered confidential and shall be subject to the provisions of Section 10.

TABLE 1

TOLERANCES FOR TRIFLURALIN

Crop	Tolerance (ppm)
Mungbean sprouts	2.0
Carrots	1.0
Alfalfa hay	0.2
Citrus fruit	0.05
Cottonseed	0.05
Cucurbits	0.05
Field corn grain fodder and forage	0.05
Forage legumes	0.05
Fruiting vegetables	0.05
Grapes	0.05
Hops	0.05
Leafy vegetables	0.05
Nuts	0.05
Peanuts	0.05
Peppermint hay	0.05
Root crop vegetables (except carrots)	0.05
Safflower seed	0.05
Seed and pod vegetables	0.05
Spearmint hay	0.05
Stone fruits	0.05
Sugarcane	0.05
Sunflower seed	0.05
Wheat grain	0.05
Wheat straw	0.05
Asparagus	0.05
Peppermint oil	2.0[1]
Spearmint oil	2.0[1]

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[1] From CFR 21 193.440; all others from CFR 40 180.207

Section 10 specifies the types of information that may be disclosed and limitations on and conditions of such disclosure. The Section also specifies penalties that may be levied upon government employees for improper disclosure of such information. This production information is provided to the Administrator in a confidential attachment to this report.

According to public data, 5,184,000 pounds of trifluralin were produced in 1966 (Mrak 1974), 21 million pounds in 1972 (von Rumker et al., 1974), more than 23 million pounds in 1974 (Keil et al., 1977), and more than 24 million pounds in 1975 (Severn, 1977).

II. Risk Analysis

A. General Toxicology, Occurrence, and Formation of N-nitroso Compounds

The NDPA contaminant in trifluralin is one member of the general chemical class known as N-nitroso compounds. This class, is subdivided into nitrosamines and nitrosamides, which are common constituents of many natural and man-made components of the environment. This section discusses the general toxicology, occurrence and formation of this class of compounds. NDPA toxicology, occurrance, formation, environmental chemistry, and biological chemistry is discussed in sections II B, C, and D of this document. Table 2 lists some common sources of N-nitroso compounds, and Table 3 summarizes information on additional pesticides that contain N-nitroso compounds.

TABLE 2

OCCURRENCE OF N-NITROSO COMPOUNDS

Source	N-nitroso Compound Detected	Concentration	Reference
Meat curing mix	N-nitrosopyrrolidine	2.5-6.0 ppm	Sen et al., 1973
	N-nitrosopiperidine	7.0-25.0 ppm	"
	N-nitrosodimethylamine	0.85 ppm	"
Bacon	N-nitrosopyrrolidine	0.004-0.025 ppm	Sen et al., 1973a
	N-nitrosodimethylamine	0.002-0.03 ppm	Sen et al., 1973a
Salami, dry sausages	N-nitrosodimethylamine	0.01-0.08 ppm	Sen, 1972
Fried bacon	N-nitrosopyrrolidine	7.0-139.0 ppb	Havery et al., 1976
Spice-cure mixes	N-nitrosodimethylamine		Havery et al., 1976
	N-nitrosopyrrolidine	50-200 ppb	"
	N-nitrospiperidine		"
Sable, salmon, shad	N-nitrosodimethylamine	0-26 ppb	Fazio et al., 1971
Cooked Bacon	N-nitrosopyrrolidine	10-108 ppb	Fazio et al., 1973
Marine salt fish	N-nitrosodimethylamine	0.05-0.30 ppm	Fong and Chan, 1973
Water	N-nitrosodimethylamine	0.05-1.0 ug/l	NEIC, 1977
	N-nitrosodipropylamine	13.0 ug/l	"
	N-nitrosopropylbutylamine	3.2-8.2 ug/l	"
	N-nitrosopyrrolidine	0.63 ug/l	"
Herbicides	N-nitrosodipropylamine	154 ppm	Fine et al., 1976
	N-nitrosodimethylamine	187-640 ppm	
Air	N-nitrosodimethylamine	40 ng/m^3	NEIC, 1977
Tobacco	N-nitrosodimethylamine	0-140 microgram/ cigarette	Rhodes & Johnson, 1972
Tobacco	N-nitrosodiethanolamine	0.1-173.0 ppb	Schmeltz et al., 1977
Cigarette smoke	N-nitrosodimethylamine	5-180 ng/cigarette	McCormick et al., 1973
	N-nitrosoethylmethylamine	To 40 ng/cigarette	"
	N-nitrosodiethylamine	To 28 ng/cigarette	"
	N-nitrosodipropylamine	1.0 ng/cigarette	"
	N-nitrosopyrrolidine	1-110 ng/cigarette	"
	N-nitrosopiperidine	1-9 ng/cigarette	"
	N-nitrosodibutylamine	3 ng/cigarettte	"
Various cosmetics	N-nitrosodiethanolamine	Trace-130 ppm	Yates & Wenninger, 1978
Cutting fluids	N-nitrosodiethanolamine	0.02-3.0%	Fan, 1976

TABLE 3

PESTICIDES THAT CONTAIN N-NITROSO COMPOUNDS[1/]

Pesticide	Contaminant	Reference
Benzthiazuran	Nitroso Derivative	a
Carbaryl	Nitroso Derivative	a
Propoxur	Nitroso Derivative	a
Fenuron	DMN	a
Atrazine	Nitroso Derivative, NDELA (0.54 ppm)	a,c
Simazine	Nitroso Derivative	a
Ziram	DMN	a
Thiram	DMN	a
Ferbam	DMN	a
Succinic acid 2,2-dimethylhydrazide	DMN	a
Oryzalin	NDPA (1 ppm) Unknown (1.5-42 ppm)	b,c
Trifluralin	NDPA (6-202 ppm)	b,c
Isopropalin	NDPA (9-87 ppm)	b,c
Butralin	NBEA Unknown, (2.4-74 ppm)	b,c
Benfluralin	NBEA 28-38.4 ppm) Unknown (30-261 ppm)	c
Maleic hydrazinde (Salt of)	NDELA (< 1 ppm) Unknown (1.4 ppm)	c
Diphenamide	DMN (< 1 ppm)	c
2,4-D (Salt of)	DMN (0.6 - 6 ppm)	b,c
MCPA	DMN (0.24 - 2.0 ppm)	b,c
MCPP	DMN (0.32 - 1.0 ppm)	b,c
2,3,6-trichlorobenzoic acid	DMN (1-359 ppm)	b,c
Profluralin	CMPNA (4 ppm)	b
Dinoseb	NDELA (217-233 ppm)	b
N-butyl-N-ethyl-2,6-dinitro-4-trifluoromethyl-aniline	BENA (8-38 ppm)	b
N,N-diethyl-2,4-dinitro-6-trifluro-methyl-1,3-phenylenediamine	DEN (100-153 ppm)	b
N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitro-benzenamine	Nitroso derivative (102-104 ppm)	b
4-(2,4-dichlorophenoxy)butyric acid (salt of)	DMN (2.5-6 ppm)	b
2,3,6-trichlorophenyl acetic acid (salt of)	DMN (18-24 ppm)	b

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[1/] This list may not be complete since it contains only those n-nitroso contaminated pesticides reported in the open literature prior to preparation of this position document. References are as follows: a) Mirvish, 1973; b) Bontoyan et al., 1979; c) Cohen et al., 1978.

Magee, et al. (1978), EPA (1977), Alexander (1976), and NAS (1978) have published general reviews of N-nitroso toxicology, formation, occurrence, and chemistry.

Nitrosamines (including NDPA) are stable at physiological pH and require metabolic transformation to active intermediates to exert their effects; nitrosamides, however, are unstable and decompose to active intermediates without being metabolized (Shank, 1975). Table 4 shows the LD_{50} of several N-nitroso compounds.

A number of scientists have studied the acute toxicity of N-nitroso compounds. Table 4 (Part II) lists these studies and their results.

Druckery et al. (1967) and IARC (1973, 1974, 1978) extensively reviewed the data on the carcinogenicity of N-nitroso compounds, and Montesano and Bartsch (1976) reviewed data on carcinogenicity versus mutagenicity of N-nitroso compounds. Shank (1975) reported that nitrosamines induce tumors in skin, nose, tongue, esophagus, stomach, duodenum, colon, lungs, bronchi, liver, pancreas, kidney, urinary bladder, brain, spinal cord, thymus, lymph nodes, and blood vessels.

Table 5 summarized the results of tests showing that N-nitroso compounds are formed in various chemical mixtures.

TABLE 4

ACUTE TOXICITY OF SEVERAL N-NITROSO COMPOUNDS

Part I:

Compound	LD_{50}[1]
Dimethylnitrosamine	27-41
Diethylnitrosamine	216
Di-n-propylnitrosamine	> 400[2]
Di-n-butylnitrosamine	1200
Di-n-amylnitrosamine	1750
Methyl-n-butylnitrosamine	130
Methyl-t-butylnitrosamine	700
Ethyl-n-butylnitrosamine	380
Ethyl-t-butylnitrosamine	1600
Ethyl-2-hydroxyethylnitrosamine	> 7500
Di-2-hydroxyethylnitrosamine	> 5000
Methylphenylnitrosamine	200
Methylbenzylnitrosamine	18
Nitrosomorpholine	282
Methylnitrosourea	180
Methylnitrosourethane	240
Nitrosohexamethyleneimine	336
Nitrosoheptamethyleneimine	283
Nitrosooctamethyleneimine	566

Part II

Compound	Effect	Reference
DMN, DEN,	Centrilobular necrosis of liver	Shank, 1975
DMN	Hepatic vein damage	Koppang and Rimeslatton, 1976 Reuber, 1975
Unspecified nitrosamines	Interference with protein synthesis	Kleihues et al. 1975 Reynolds, 1977 Plapp, 1975
DMN	Necrosis of seminiferous epithelium	Hard and Butler, 1970
DMN	Fetotoxicity	Druckery, 1974

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[1] LD_{50} units mg/kg, single oral dose, adult male rats (Shank, 1975).
[2] Male and female Syrian golden hamsters.

Table 5

Formation of N-nitroso Compounds

Nitroso Compound Formed	Comments	Reference
N-nitrosodiethanolamine	Industrial grinding fluid incubated under gastric conditions	Zingmark and Rappe, 1976
Various N-nitroso compounds	Amines mixed with nitrous acid	Lijinsky and Singer, 1975
Various N-nitroso compounds	Quaternary ammonium compounds and related tertiary amines incubated *in vitro* with sodium nitrite	Fiddler et al., 1972
DMN	Dimethylamine and sodium nitrite incubated with rat intestinal bacteria under anaerobic conditions	Klubes et al., 1972
DMN	*In vitro* mixing of certain pesticides with nitrite	Egert and Greim, 1976 1976a
DMN	*In vitro* and *in vivo* mixing of thiram, ziram, ferbam, DSMA with sodium nitrite	Sen et al., 1975
DMN	*In vivo* mixing of ziram and sodium nitrite	Eisenbrand et al., 1975
Various N-nitroso compounds	*In vitro* mixing of atrazine, simazine, propoxur, carbaryl, benzthiazuron with sodium nitrite	Eisenbrand et al., 1975
Various N-nitroso compounds	Injection of piperidine, pyrrolidine with sodium nitrite into infected rat bladders	Hawksworth and Hill, 1974
Various N-nitroso compounds	Formation in pesticide treated soil (theoretical analysis)	Mittleman, 1977

The following sections discuss studies of the environmental fate, routine environmental monitoring for chemical residues, and the biological fate of trifluralin and its specific N-nitroso contaminant, NDPA.

B. Environmental Fate

1. Trifluralin

Several researchers have studied the degradation of trifluralin in soil (Parka and Tepe, 1969; Savage, 1973; and Golab and Amundson, undated). In general, these scientists found that trifluralin did not accumulate in most soils after repeated annual applications. However, very low residues may persist in certain soils, both in the field (West and Day, 1977; Probst et al., 1967) and under laboratory conditions (Kearney, 1974-75).

Many factors influence the persistence of trifluralin and its degradation in soil. These factors include the soil's organic matter content, its moisture and temperature, and the methods by which trifluralin was incorporated into it. According to Mosier and Saunders (1977), trifluralin is highly resistant to leaching. Boyd (1978) reported that trifluralin is strongly adsorbed to organic matter.

According to the available data, trifluralin does not readily run off from treated fields. Willis et al. (1975) studied the rate at which several herbicides, including trifluralin, were lost from surface drainage waters in Louisiana. Runoff volumes differed due to variations in plant canopy, soil texture, and soil surface conditions, and runoff volumes clearly influenced herbicide loss. Only 0.05% of the total trifluralin which was applied to cotton or soybeans was lost through runoff in the three months following application.

Trifluralin is also readily volatilized and photodegraded in the environment. Spencer and Cliath (1974) and Parochetti and Hein (1973) indicated that trifluralin volatilization rates increase significantly with increasing temperature and soil moisture.

Soderquist et al. (1975) reported that trifluralin vapor is stable in the dark but degrades rapidly to dealkylated dinitrotoluidines, cyclic diol-benzimidazole precursors (benzimidazolines, benzimidazole-N-oxides), and benzimidazole when exposed to light in a photoreactor. After 12 days of irradiation, the principal products were the benzimidazoles. Leitis and Crosby (1974) reported a photodecomposition mechanism for trifluralin involving oxidative dealkylation, nitro reduction, and cyclization.

Parochetti and Hein (1973) reported no photochemical degradation of trifluralin on the soil surface over a 24-hour period, based upon residual herbicidal activity; however, chemical analysis demonstrated that photodecomposition had, in fact, taken place in this study. In addition, Parochetti and Hein (1973) found that trifluralin adsorbed to soil in a petri dish photodegraded with a half-life of 2.2 hours.

Kearny et al. (1974-1975) reported tentative results of studies which indicated that trifluralin is metabolized in soil to the same dealkylated toluidines and benzimidazole compounds (seven months after treatment) as from photodecomposition. They gave no quantitative results.

2. N-nitrosodipropylamine (NDPA)

The Agency reviewed studies on the environmental fate of NDPA in order to assess the extent of human exposure to NDPA from Treflan use. In general, NDPA photodegrades in soil, water, and as a vapor, but it doesn't readily hydrolyze, and it volatilizes from soil only slightly.

Tate and Alexander (1975) reported that NDPA has a half-life of about 40 days in silt loam soil. However, the soil in this experiment lost little of the compound over the first seven to ten days of incubation; the authors noted that this time lag might indicate microbial degradation of NDPA.

Gray and Saunders (1977, 1977a) determined that NDPA degrades more slowly under anaerobic than under aerobic conditions.

In a field leaching study, Mosier and Saunders (1977) incorporated NDPA into sandy and silty clay loam soil columns. The assay indicated that NDPA was being lost by degradation, volatilization, and some leaching. NDPA also leached readily in a laboratory study using sandy and silty clay loam soils; from 89% to 96% of added ^{14}C-NDPA was found in the leachate (Saunders, 1977).

West and Day (1977) analyzed soil which had been treated with NDPA contaminated Treflan for NDPA immediately after treatment. They found no NDPA at a level of detection of 0.05 to 0.20 ppb (50-200 ppt). This is not surprising since at an application rate of 1.0 pound active ingredient (containing 6 ppm NDPA) per acre, the upper 6 inches of soil would contain only 6 ppt (parts per trillion) NDPA, assuming a soil density of 0.06 lb/in ^{3}(Mittelman, 1978c).

NDPA does not readily hydrolyze. In experiments by Saunders (1976), NDPA in solution maintained at 51°C and pH 3-9 had not hydrolyzed after 32 days.

When exposed to ultraviolet (UV) light, however, NDPA in solution is readily photolyzed. Mosier and Saunders (1977a) exposed an NDPA solution in lake water to sunlight and found that the NDPA had a half-life of about 3 hours.

Day and West (1977) analyzed pond water from a field treated six months earlier with Treflan EC (emulsifiable concentrate) and found no detectable NDPA residues. They also artificially irradiated NDPA in distilled water (2.2 ppm) in the laboratory. Under these conditions, the NDPA had a half-life of about 45 minutes.

NDPA also photodegrades in the vapor phase. Gray and Saunders (1977b) estimated the half-life of NPDA in natural sunlight to be 20 minutes.

After surface application to soil, however, NDPA is apparently less photodegradable. In dry soil field experiments performed by Mosier and Saunders (1977b), about 90% of the NDPA remained eight hours after application. Mosier and Saunders also performed wet soil experiments in which about 73% of the NDPA remained 0.25 hours after application, and nearly 47% remained after eight hours. These experiments indicate that NDPA volatilizes at a faster rate from moist soil than from dry soil.

Oliver (unpublished data, 1978 USDA) incorporated radiolabeled NDPA into the top 7.5 cm of various diverse soil types enclosed in glass chambers and passed air over the soil surface. NDPA volatilized from the soil at a decreasing rate throughout the 192 hours during which the system was monitored. The cumulative total of volatilized NDPA at 24 hours was 2.35%; at 192 hours it was 3.77%.

C. Residues

Trifluralin has been detected in several routine environmental monitoring programs. The data available from these programs were too limited to use in the Agency's exposure or risk calculations, however. NDPA has not been detected in any of the monitoring programs.

The National Soils Monitoring Program (NSMP) (Kutz 1977) sampled agricultural sites between FY 1969 and FY 1974. Trifluralin was applied to 72 of 1,684 sample sites in 1969 and 88 of 1,165 sites in 1974; more than 85% of the applications during this time were either to soybeans or to cotton. The number of trifluralin applications increased steadily between FY 1969 and FY 1974. This reflected the growing trend toward chemical, rather than mechanical, weed control by farmers.

Trifluralin residues were detected in an increasing number of agricultural soil samples in the National Soil Monitoring Program (NSMP) between FY 1969 and FY 1973. The arithmetic mean concentration of trifluralin in the soil samples (less than 0.01 ppm), however, did not change significantly during this period.

Trifluralin residues in crop samples collected from NSMP monitoring sites from FY 1969 to FY 1973 were found in three of 41 crop materials: cotton stalks, sorghum stalks, and soybeans. These values ranged from 0.01 to 0.31 ppm; most were less than 0.1 ppm. A total of 3,576 samples were analyzed during this period.

The Urban Monitoring Program has sampled 42 urban areas since 1971. This program has detected trifluralin in only two urban locations, San Francisco, California and Springfield, Illinois, at an average level of 0.05 and 0.01 ppm, respectively (Kutz, 1977).

Air was monitored for pesticides in 1970 and 1972 in predominantly agricultural areas of 16 States; trifluralin was found in 11 of the States (Kutz, 1977). The maximum values detected ranged from 1.1 to 30.3 nanograms (ng) per cubic meter of air.

The Market Basket Survey of the Food and Drug Adminstration (FDA) monitors pesticide residues in a sample daily diet of an average 16 to 19-year-old American male in various regions of the country. To date, trifluralin has not been detected in this survey (Corneliussen 1978).

The FDA surveillance and compliance program's multiresidue method can detect trifluralin at 0.01 ppm or greater in commodities. In 1975 trifluralin was not detected in the 8,009 samples analyzed in that program. In 1976 trifluralin was found at 0.10 ppm in one parsnip sample and at 0.03 and 0.04 ppm in two carrot samples out of a total of 8,416 samples. In 1977 trifluralin was detected at 0.02 ppm in one potato sample, at 0.04 ppm in one parsnip sample, and in 16 carrot samples at levels ranging from 0.03 ppm to 0.19 ppm. There were 6,674 samples analyzed in that program in 1977.

Trifluralin has not been reported in the APHIS (USDA) "Objective Phase Biological Residue Report (1973-1976)". EPA's Storet System, which maintains data on water quality parameters, has no data on trifluralin.

The National Soils Monitoring Program, FDA's Market Basket Survey, and FDA's surveillance and compliance program for food and feeds have not monitored for NDPA (Corneliussen, 1978), nor was NDPA reported on the APHIS (USDA) "Objective Phase Biological Residue Report (1973-1976)". EPA's Storet System of water quality parameters currently contains no monitoring data for NDPA; however, NDPA is one of the compounds on the List of Priority Pollutants which EPA will monitor in water.

D. Biological Fate

The ability of living organisms to absorb, translocate, and metabolize a compound is important in determining whether various toxic effects occur. Since no studies of the biological fate of trifluralin and NDPA in humans exists, a number of studies with various animal species were reviewed in order to determine the fate of these compounds in living organisms. These and the biological fate of trifluralin ad NDPA in plants are discussed below.

1. Trifluralin

Generally, trifluralin is not readily translocated to the above-ground portions of most tolerant plants. However, certain root crops, such as carrots, onions, and garlic, have been shown to absorb and metabolize the compound (Probst et al., 1967). Peanut and sweet potato leaf extracts also metabolize trifluralin. Even though some plants may metabolize trifluralin, significant residues of trifluralin or its degradation products reportedly do not accumulate in edible portions of plants (Probst et al., 1975).

Marine invertebrates metabolize trifluralin through the pathways of oxidation, reduction, hydrolysis, and conjugation (Garnas, 1976). Spacie (1976) found that trifluralin accumulated in the fat of three species of fish exposed to 874 ppt trifluralin in an industrial effluent. Levels decreased in two species by 40% to 83% after activated carbon filtration of the industrial effluent started. The fish exhibited no acute effects during this investigation.

In degradation studies with ruminant animals, trifluralin was fed to a lactating cow and a goat; blood, milk, feces, and urine from the treated animals were then analyzed for trifluralin or its metabolites. No residues were detected in milk or blood. Detectable residues were found only in feces of a cow fed 1,000 ppm trifluralin for 16 days, and in the feces (81.2%) and urine (17.8%) of a goat fed 1 ppm trifluralin for 16 days. Little trifluralin was metabolized; most passed through the animals unchanged (Golab et al., 1969). Williams and Feil (1971) found that two of 12 species of rumen bacteria tested metabolized trifluralin.

Male Harlan-Wistar rats excreted 80% of a single 100 mg/kg oral dose of trifluralin, in the feces (Emmerson and Anderson, 1966). Female dogs also metabolized trifluralin.

Nelson et al. (1977) also studied the in vitro metabolism of trifluralin and other dinitroaniline herbicides in rat liver microsome preparations. In addition to other metabolites, Nelson detected minute amounts of a possible benzimidazole compound from trifluralin metabolism for the first time in a mammalian system.

2. NDPA

Nitrosamines are reportedly metabolized relatively rapidly by animals (Office of Research and Development, 1977). In the absence of metabolic enzymes, they are chemically stable under physiological conditions; metabolic activation to a reactive intermediate is necessary for adverse effects to occur (Montesano and Bartsch, 1976).

Metabolism by oxidative dealkylation beginning at the alpha carbon of one chain ultimately leading to a reaction with cellular macromolecules has been proposed by several scientists (Druckery et al., 1969; Brusik and Mayer, 1973). Krueger (1971, 1973, 1973a) found that NDPA undergoes beta hydroxylation ultimately producing alkylating compounds that react with nucleic acids in the rat liver. Blattman and Preusman (1973) reported omega oxidation and omega-1-oxidation in a study of rat urinary metabolism of NDPA. The oxidation scheme is but one potential mechanism involved in dialkylnitrosamine metabolism. Three other schemes involving protolytic fragmentation have been suggested to explain experimental observations which are inconsistent with the oxidation model (Olah et al., 1975).

Samples of soybeans, cotton, cauliflower, carrots, and alfalfa grown in soil treated with Treflan contaminated with from 78 to 500 ppm NDPA had no detectable levels of NDPA at a test sensitivity of 0.10-0.20 ppb (West and Day, 1977a). When Berard (1977) grew soybean plants in a nutrient solution containing ^{14}C-labeled NDPA, about 25% of the applied radioactivity translocated to the soybean plants; however, only 1% of the radioactivity was identified as NDPA after seven days. Berard did not attempt to identify the remaining radioactivity. Berard and Rainey (1977) performed a field study in which soybeans were grown in soil treated with the equivalent of 5,000 ppm NDPA. They detected less than 0.3 ppb ^{14}C expressed as NDPA equivalent at 21 and 49 days, and detected no residue in soybean seed after 119 days.

NDPA was readily absorbed and passed into goat's milk after a single oral dose of 30 mg/kg body weight. The detectable quantity of NDPA in milk peaked at 5.8 mg/kg after 0.5 hours. After 24 hours only a trace remained, and none was detected at 36 hours. NDPA levels in the blood were 1.578 mg/kg after one hour and 0.0004 mg/kg after six hours (Juszkiwicz and Kowalski, 1975).

E. Exposure Analysis

This section discusses only the exposure to NDPA which is associated with the use of formulated trifluralin, not with exposure to trifluralin itself. This is because the primary concern relative to the toxicity of this compound (for RPAR purposes) is associated with its NDPA contaminant. Trifluralin exposure is discussed briefly in the appropriate sections of this document which present evaluations of specific toxic effects and in full in the Agency's exposure report for trifluralin and NDPA (Mittelman, 1978).

1. Exposure During Application

Humans who use trifluralin and are therefore potentially exposed to NDPA include agricultural and nursery workers who mix, load, apply, and incorporate the compound into the soil; fieldworkers; domestic users; and the population at large. The Agency has estimated NDPA exposure from Treflan use, and this provides the basis for the estimates presented here (Mittelman, 1978).

Exposure estimates in this document are given for workers on average size farms for each of the uses assessed. The Agency estimated the number of workers who apply Treflan from Agency information, Doane Agricultural Statistics data, personal communications with USDA, university and other experts, and the registrant. In arriving at the estimate, the Agency assumed that there is only one private applicator per farm. Figures derived in such a fashion may underestimate exposure to applicators on larger farms. However, large farms use more efficient apparatus, larger spray booms, faster tractors with enclosed cabs, larger spray tanks, and several applicators, all of which tend to lessen any increase in exposure.

The extent of exposure to applicators, incorporators, mixers, and loaders depends on their rate of respiration, time exposed, climatic condition (wind speed, ambient temperature, humidity), soil conditions (soil temperatures, organic matter content of the soil, moisture content), rate of trifluralin application, NDPA content of the trifluralin, and other variables. Of the factors affecting NDPA exposure, total time exposed is the most important. This factor, in turn, depends upon the total acreage involved, speed of performing constituent operations, condition of the field, and the apparatus used. Time is thus a highly variable parameter.

Exposure estimates were based on studies reported in the open literature and field monitoring studies performed by the registrant. The Treflan EC used in field monitoring studies contained from 3.5 to 6.4 ppm NDPA (Day et al., 1978). In these studies sources of exposure, which included vapor inhalation, particulate inhalation/ingestion, and recovery from the soil surface, were effectively measured for NDPA. Due to the volatility and photolability of NDPA, monitoring for dermal exposure was not successful and resulted in extremely low NDPA recovery.

Results of vapor phase sampling studies indicate an average concentration of 0.0047 ug NDPA/ m^3 of air in the breathing zone during application and simultaneous incorporation plus about 0.0001 ug NDPA/m^3 adsorbed to particulate matter that can be inhaled or ingested during soil treatment. During mixing and loading, the concentration of NDPA in the air was determined to be 0.012 ug/m^3. The Agency calculated vapor/particulate NDPA exposure via inhalation and ingestion from the following:

$$E_{TI} = (H_a)(C_a)(R) + (H_m)(C_m)(R)$$

where:

E_{TI} = Total exposure (inhalation/ingestion)

H_a = Hours applying trifluralin/year

C_a = Concentration of NDPA in the air during application/incorporation = 0.0048 ug/m^3

R = Respiratory rate = 1.2 m^3/hr

H_m = Hours mixing/loading trifluralin/year

C_m = Concentration of NDPA in the air during mixing/loading = 0.012 ug/m^3

Exposure for private farmers incorporating custom-applied Treflan was estimated similarly, but the quantity [$(H_m)(C_m)(R)$] was omitted.

The Agency calculated dermal exposure to applicators, incorporators, mixers, and loaders from results obtained in an experiment using an artificial adsorber. Such an estimate is inexact, but it is likely to be closer to actual levels than an estimate calculated on a worst-case basis or using zero from the unsuccessful dermal monitoring studies (Day et al., 1978). Hourly dermal exposure was calculated to be 0.083 ug/hr (Mittelman, 1978). The Agency then calculated total dermal exposure for applicators, incorporators, mixers, loaders, and private farmers incorporating custom-applied Treflan as follows:

$$E_{td} = (H_a)(E_{hd})$$

where:

E_{td} = Total exposure (dermal)

H_a = Hours applying trifluralin/year

E_{hd} = Hourly dermal exposure during application = 0.083 mg/hr

The true dermal exposure is difficult to assess due to the absence of an acceptable method of measuring this factor. Dermal exposure is important since it is generally much higher than inhalation exposure. These exposure estimates concern only that amount of NDPA deposited upon the skin. The risk estimates discussed later in this document adjust the total NDPA dermal exposure estimate for the proportion of NDPA that is thought to be absorbed.

Table 6 summarizes the total NDPA exposure to persons who apply Treflan (contaminated with 3.5 to 6.4 ppm NDPA) to various crops. Exposure to private and commercial applicators is presented separately. Private applicators apply and incorporate the material whereas commercial applicators normally only apply the material. The farmer must then incorporate this commercially-applied material within 24 hours. Table 6 groups exposure to private applicators/ incorporators and incorporators of commercially applied Treflan together (Group I), and lists commercial applicators (Group II) as a separate category. Differences in total NDPA exposure estimates between private workers who perform all kinds of application operations and those who only incorporate commercially-applied Treflan are small. Incorporators of commercially-applied material do not mix and load, but these operations are of short duration. For example, in soybeans, private applicators of Treflan receive a total annual exposure of 1.45 ug NDPA, whereas private individuals incorporating commercially-applied Treflan receive 1.42 ug NDPA per year, a difference of only 0.03 ug.

2. Exposure During Re-entry

While primary NDPA exposure is likely to occur to applicators, workers re-entering treated fields may also be exposed to NDPA as a vapor or NDPA adsorbed to particles of soil. Exposure from this source was evaluated by two different methods.

TABLE 6

ANNUAL NDPA EXPOSURE TO AGRICULTURAL WORKERS INVOLVED IN TRIFLURALIN APPLICATION OPERATIONS

Application Site	Total Number of Individuals	Annual NDPA Exposure (micrograms) Inhalation/ Ingestion	Dermal	Total
Group I[1]				
Soybeans	193,138	0.12	1.33	1.45
Cotton	63,954	0.11	1.08	1.19
Fruits and Vegetables				
Tomatoes	13,490	0.04	0.42	0.46
Potatoes	1,800	0.05	0.50	0.55
Dry Peas	202	0.13	1.41	1.54
English Peas	2,776	0.04	0.42	0.46
Field Peas	156	0.04	0.42	0.46
Cole Crops[2]	4,162	0.04	0.50	0.54
Carrots	657	0.07	0.83	0.90
Peppers	2,267	0.02	0.17	0.19
Celery	166	0.11	1.33	1.44
Cucumbers	3,030	0.01	0.17	0.18
Watermelons	2,718	0.02	0.25	0.27
Cantaloupes	335	0.03	0.33	0.36
Mints[3]	55	0.18	2.16	2.34
Okra	856	0.02	0.17	0.19
Beans[4]	23,689	0.07	0.75	0.82
Other Field Crops				
Peanuts	4,474	0.06	0.59	0.65
Sugar Beets	5,178	0.14	1.66	1.80
Sunflowers	5,523	0.13	1.50	1.63
Miscellaneous Crops				
Trees and Vines[5]	3,985	0.07	0.75	0.82
Hops	51	0.23	2.74	2.97
Greens[6]	3,259	0.01	0.17	0.18
Dill	16	0.08	0.91	0.99
Alfalfa	320	0.07	0.83	0.90
Spring Wheat	890	0.34	4.07	4.41
Mustard for seed	68	0.12	1.33	1.45
Safflower	933	0.27	3.24	3.51
Sugar Cane	116	0.40	4.65	5.05

Group II				
All Crops (Commercial Applicators)	3,800	0.14	1.74	1.88
TOTAL	342,064			

1/ These estimates apply to both farmers who mix, load, apply, and incorporate the pesticide as well as those who only incorporate commercially-applied Treflan.

2/ Cole Crops: brussel sprouts, cauliflower, cabbage, broccoli.

3/ Mints: spearmint, peppermint.

4/ Beans: castor, snap, lima, southern peas, guar, mung, dry

5/ Tree and Vine: grape, lemon, grapefruit, nectarine, orange, tangelo, tangerine, almond, apricot, peach, pecan, plum, prune, walnut.

6/ Greens: collards, kale, turnip, mustard.

In the first method, Mittelman (1978) calculated a 3:1 ratio of recoverable volatilized NDPA in the air between a model system (Oliver, USDA, unpublished data, 1978) and a field monitoring system (Day et al., 1978) (discussed earlier in Section II. B.). From this ratio, the Agency calculated the quantity of volatilized NDPA for 12, 24, 48, 96, and 192 hours post-treatment, thus:

Time (hours)	NDPA In Air ng/m3
6-12	1.01
12-24	0.68
24-48	1.75*
48-96	0.56
96-192	0.39

The concentration of NDPA in the air was then evaluated for re-entry periods (the interval between the time a pesticide is applied and the time a worker re-enters the field) in soybeans, cotton, beans, tomatoes, cole crops, and tree and vine crops. Tables 7, 8, 9, and 10 summarize these findings. From this analysis the Agency determined that there would not be quantifiable inhalation exposure to NDPA from the air over treated soybean and cotton fields at the average time of first re-entry (day 14 and day 30, respectively). Based on this model, the total annual NDPA exposure for a field worker performing all re-entry activities in the remaining crops assessed would be:

Crop	Total Exposure (Dermal+Inhalation; ug/Year)
Beans	0.05
Tomatoes	0.09
Tree and Vine	0.24
Cole Crops	0.09

---

*/ Water was applied to soil at this point, increasing NDPA volatilization from soil.

TABLE 7

WORKER RE-ENTRY EXPOSURE TO NDPA IN BEANS
(ug/year)

Activity	Average Days After Treatment (Range)	Hours Spent In Activity Per Year	Concentration In Air (Micrograms/m^3)	Inhalation Exposure	Dermal[2] Exposure	Total Exposure
Second Incorporation[1]	7 (0-14)	6	0.00039	0.003	0.042	0.05
Planting	18 (0-35)	13				
Tillage	42 (28-56)	20				
Irrigation	56 (28-84)	8				
Harvest	98 (49-147)	32				
						TOTAL = 0.05

[1] 10% of total is bedded cultured requiring no second incorporation.
[2] This is estimated to be 15 times inhalation exposure.

TABLE 8

WORKER RE-ENTRY EXPOSURE TO NDPA IN TOMATOES
(ug/year)

Activity	Average Days After Treatment (Range)	Hours Spent In Activity Per Year	Concentration In Air (Micrograms/m^3)	Inhalation Exposure	Dermal[2] Exposure	Total Exposure
Seeding[1]	3 (0-7)	8	0.00056	0.005	0.081	0.09
Tillage (One time)	42 (28-56)	5				
Irrigation (Four times)	45 (7-84)	8				
Hand Hoeing	35 (28-42)	125				
Harvest	105 (90-120)	16				
					TOTAL =	0.09

1/ Most tomatoes are directly seeded (90%) and do not require second incorporation.
2/ This is estimated to be 15 times inhalation exposure.

TABLE 9

WORKER RE-ENTRY EXPOSURE TO NDPA IN TREE AND VINE CROPS
(ug/year)

Activity	Average Days After Treatment (Range)	Hours Spent In Activity Per Year	Concentration In Air (Micrograms/m^3)	Inhalation Exposure	Dermal[2] Exposure	Total Exposure
Second Incorporation	3 (0-7)	6	0.00056	0.004	0.06	0.06
Planting[1]	7 (0-14)	24	0.00039	0.011	0.165	0.18
Irrigation (Eight times)	45 (7-210)	16				
Tillage and Spraying	134 (28-240)	66				
Harvest	210 (150-270)	224				
					TOTAL =	0.09

1/ Fifty percent of total acreage consists of new planting.
2/ This is estimated to be 15 times inhalation exposure.

TABLE 10

WORKER RE-ENTRY TO NDPA IN COLE CORPS
(ug/year)

Activity	Average Days After Treatment (Range)	Hours Spend In Activity Per Year	Concentration In Air (ug/m3)	Inhalation Exposure	Dermal[2/] Exposure	Total Exposure
Second Incorporation	0 (0-7)	3	0.00056	0.002	0.030	0.03
Direct Seedling[1/]	3 (0-7)	6	0.00056	0.004	0.060	0.06
Tillage (Two times)	45 (28-63)	6				
Hand Hoeing	42 (28-56)	16				
Irrigation (Six times)	45 (7-84)	12				
Harvest	105 (84-126)	44 (225-1100)				
Total						0.09

1/ Sixty percent of total acreage is directly seeded; transplanting requires about 96 hours per worker.
2/ This is estimated to be 15 times inhalation exposure.

In this model the Agency chose not to include a factor for photodegradation of NDPA, a well-established characteristic discussed in Section II (B) of this document. Therefore, in the second model the Agency incorporated factors for photodegradation into these calculations, which resulted in an estimate of even lower levels of NDPA in the air at times when workers are in the field.

In order to estimate such NDPA exposure considering photodegradation the Agency used the study by Oliver previously discussed (USDA, 1978). In that study by Oliver NDPA volatilization from soil which had been treated with trifluralin containing 18 ppm NDPA was monitored over an eight-day period. In the first six hours 1.46% of the NDPA had volatilized into the air above the soil, and after eight days a total of 3.77% of the applied NDPA had volatilized. Very little additional NDPA volatilized after two days.

An upper limit to the air concentration of NDPA was calculated from an assumed application rate of 1.29 pounds of active ingredient per acre, 3.5 ug NDPA/g active ingredient, a volatilization rate of 1.46% of this material into a 2-meter layer of air above the field in the first six hours, and no dilution from air convection. The concentration was estimated to accumulate to 8.4 nanograms NDPA/m^3 of air in the absence of photodegradation. However, with a photodecomposition half-life of twenty minutes, the concentration would likely decrease to $(1/2)^{18} \times (8.4 \text{ nanograms/m}^3)$, which is a negligible amount.

Dermal NDPA exposure from contact with the compound in soil during re-entry to treated fields is theoretically possible. This quantity is difficult to estimate because of the extreme variability of the field activities performed, the degree of physical contact with the soil by workers, the amount of exposed body area, the length of time exposed, and the partitioning co-efficient of trifluralin between soil particles and the part of the human body which comes into contact with the soil. This exposure is expected to be low, if it exists at all, since the level of NDPA in the product is already low and application disperses it still further. To quantify this, an upper limit to the level of potential exposure to fieldworkers was calculated. West and Day (1977) found up to 0.19 ug NDPA/kg soil 26 days after application of 0.75 lb active ingredient/acre. The trifluralin used contained from 78-252 ppm NDPA.

If it is assumed that a worker entering the field has a total uncovered skin surface area of 2,900 cm^2 (Mittelman, 1978), and that a uniform layer of soil forms a film on the uncovered skin 1.0 mm thick, the maximum quantity of NDPA can be calculated thus:

$$S = (SA_B)(T)(Q)$$

where:

S = Quantity of soil on exposed skin (grams)

SA_B = Exposed body surface area

T = Soil layer thickness on skin area

Q = Quantity of soil in a cubic meter (assuming a soil density of 3.0)

$$S = (0.29m^2)(0.001m)(3,000,000\ g/m^2) = 870\ g$$

Then the NDPA in the soil adhering to the exposed skin would be calculated thus:

$$\text{NDPA in soil on skin} = (S)(R_s)$$

where:

S = Quantity of soil on exposed skin (kilograms)

R_s = NDPA soil residue (based on old trifluralin having from 78-252 ppm NDPA contamination)

$$\text{NDPA in soil on skin} = (0.87\ kg)\ (0.19\ ug/kg\ in\ soil) = 0.1653\ ug$$

By this model, 0.1653 ug NDPA would be in the soil adhering to the skin. However, only an unknown fraction of this amount is actually expected to translocate into the body. This would depend upon the amount of NDPA that moves from the soil to the skin surface, the amount that penetrates into the skin (assumed to be about 22% by CAG), the actual contamination level in the product (currently less than 1 ppm as opposed to 78-252 ppm in the study leading to the 0.19 ug NDPA residue), the photodegradation of NDPA in the soil or on the skin, and other factors. By applying the penetration factor of 22%, the level decreases to about 0.036 ug during re-entry if all NDPA adsorbed onto the soil particles is assumed to move from the soil to the skin surface.

3. Exposure to Other Workers

In addition to these large groups, several smaller groups use or are exposed to trifluralin products: nursery workers, aerial applicators, flaggers, and landscape contractors. Exposure of aerial applicators and flaggers to NDPA is unknown but negligible compared to that received by ground applicators, because little trifluralin is applied aerially (Mittelman, 1978).

A small but unknown number of individuals apply Treflan EC to nurseries. This product is applied by procedures similar to those used on agricultural sites. Exposure to these nurserymen is not likely to differ from that to applicators for other agricultural uses.

In addition, a small number of nurserymen and landscape contractors apply Treflan 5% granular product. There are no data with which to quantify potential inhalation exposure from this use. Assuming normal care is used, it is unlikely that significant dermal exposure would occur during application of this formulation (due to lack of contact with the granules by the applicator during application (Mittelman, 1978).

4. Potential Formation of N-nitroso Compounds After Treflan Application

Dipropylamine is expected to be a carryover product at levels to 10 ppm during production of trifluralin. Day et al. (1977) found that dipropylamine, a material used in the synthesis of Treflan, reacted slowly with the nitrite present in liquid fertilizers to form low concentrations of NDPA (0.002 ppm) over a 42-hour period. However, 48 hours after mixing Treflan with various liquid fertilizers, Day detected no increase in the NDPA content of the Treflan.

One of trifluralin's photodecomposition products is 2,6-dinitro-N-n-propyl-trifluoro-p-toluidine (Leitis and Crosby, 1974; Soderquist et al., 1975). A potential N-nitroso product in soil would be 2,6-dinitro-N-nitroso-N-n-propyl-trifluoro-p-toluidine. Golab and Althaus (undated) applied ^{14}C-labeled trifluralin to field plots at the rate of 1.5 lb active ingredient/acre to soil fertilized with 500 lb/acre of 6-24-24 fertilizer. Analysis by Thin Layer

Chromatography and Liquid Scintillation Counting four months after application revealed a potential concentration of 0.08 ppb of such a dealkylated N-nitroso compound in soil. Since this level was lower than the reliable sensitivity of the test method (0.1 to 0.5 ppb), it is not certain that the compound is actually formed in the soil. Even assuming that the compound is formed, the maximum level in soil would be 0.08 ppb; and, therefore, human exposure is likely to be insignificant (Mittelman, 1978).

5. Exposure From Products Used Around the Home

A number of products containing trifluralin are formulated for use around the home. The concentration of trifluralin in these products is generally low; only a few contain greater than 2.8% trifluralin. Because of the low use of trifluralin in this group, low concentration, application procedures which lead to little physical contact, and the small size of treated areas involved, the Agency does not expect that homeowners would be exposed to measurable levels of NDPA from such uses.

NDPA levels reported to the Agency for a number of home use products produced from old manufacturing use trifluralin (having much higher NDPA levels than that presently produced) are summarized in Table 11. Such products should contain even less NDPA as the new trifluralin which has less than 1.0 ppm NDPA is introduced into commerce during 1979.

TABLE 11

(Mittelman, 1978b)

NDPA LEVELS IN PRODUCTS FORMULATED FROM OLD TRIFLURALIN

Trifluralin In Formulated Products (%)	Concentration of NDPA Reported (ppm)
1.47	< 0.1
1.75	0.5 - 0.8
3.0	< 0.1
5.0	0.45
9.0	0.6

Note: The level of detection was 0.1 ppm in these analyses.

Two of these analyses showed no detectable residues of NDPA in the product. Those remaining contained an amount that would be below the level of detection when applied to the soil.

6. Dietary Exposure

a. Background

This discussion of potential dietary exposure is confined to NDPA residues in treated crops since the cancer risk (the only quantifiable risk in this assessment) is a property of the NDPA contaminant of trifluralin.

West and Day (1977a) could not detect NDPA at a test sensitivity of 0.10 to 0.20 ppb in crops grown on agricultural land treated for successive years with Treflan EC, which contained as much as 450 ppm NDPA. Crops analyzed included soybeans, mature cotton seed, mature cauliflower (fruit and leaves), mature carrots (roots and tops), volunteer alfalfa, and cotton seedlings.

Laboratory studies, however, have indicated that nitrosamines can be taken up by plants, at least during the short-term. In a study by Dean-Raymond and Alexander (1976) during which relatively large amounts of dimethylnitrosamine (DMN)were added to soil in clay pots, lettuce and spinach assimilated DMN during a 2-to 15-day interval in proportion to the amount added to the pots in which they grew. Berard (1977) grew soybean plants with their roots immersed in a nutrient solution containing 0.17 ppm NDPA (6.72 ug/container). The 10-day-old plants took up 0.3 to 0.8 ug equivalents of radio-labeled NDPA over a seven-day treatment period.

Berard and Rainey (1977) planted soybean seeds in soil treated with Treflan EC, to which radio-labeled NDPA had been added at a concentration equivalent to 5,000 ppm. These soybean plants contained 0.00025 ppm and 0.00012 ppm NDPA equivalents after 21 and 49 days, respectively. In this test, control plants contained background radioactivity levels equivalent to 0.00010 ppm and 0.00006 ppm NDPA at the same sampling time. In addition, seed from soybean plants harvested 119 days after the initial soil treatment with Treflan contained no radioactive residue.

b. Exposure Estimate

To maintain consistency within the various exposure estimates, the Agency estimated dietary residues based on an NDPA contamination level of 5 ppm in the formulated product (Treflan EC). At this level in the Treflan EC formulation, the ratio of trifluralin to NDPA is 89,000 to 1. The Agency used this ratio to calculate the exposure to NDPA from data on trifluralin. To estimate exposure to Treflan containing other levels of NDPA contamination, this ratio would be changed as appropriate.

Trifluralin can be recovered in the market basket survey procedures of the FDA, but no such residues have been reported. However, there are a few reports of trifluralin found by the FDA in its surveillance and compliance programs for the period 1975-1977. No residues were found in surveys by APHIS of USDA. Furthermore, there are no known reports of residues of NDPA found in any of these surveys. For these reasons other means were used to develop the "probable case" exposure (summarized in Table 12 for trifluralin and NDPA). This method uses information on the percentage of crop acreage treated, published information on trifluralin tolerances, data on food factors, and an established trifluralin to NDPA ratio of 89,000 to 1 in formulated Treflan. The total probable dietary exposure to NDPA is about 1.92 x 10^{-9} mg/kg body weight/day (Beusch and Johnson, 1978).

For comparison, available data on NDPA residue analyses of the few crops listed above (West and Day, 1977a) were used to calculate a residue level based on the sensitivity of the analytical method used. In so doing, it was necessary to assume NDPA was present in crops at the level of detection

TABLE 12

POTENTIAL DIETARY EXPOSURE TO NDPA

Food Type	Maximum Daily NDPA Intake X_i (x 10^{-9}) mg/kg of Diet[1]
Asparagus	0.79
Carrots	21.74
Citrus Fruit	1.69
Corn, grain	5.62
Cottonseed	0.59
Curcurbits	
Cantaloupe	0.29
Cucumber	1.19
Watermelon	2.41
Fruiting Vegetables	
Peppers	0.26
Tomato	11.09
Grapes/Raisins	0.22
Hops	0.04
Leafy Vegetables	
Broccoli	0.37
Brussel Sprouts	0.11
Cabbage	2.76
Cauliflower	0.22
Celery	0.64
Collards	0.43
Kale	0.16
Mustard Greens	0.29
Turnip Greens	0.16
Mung Beans	6.74
Nuts	0.04
Peanuts	0.40
Peppermint	0.52
Root Crop Vegetables	
Potatoes	1.62
Safflower	0.17
Seed/Pod Vegetables	
Beans	8.66
Soybeans	1.95
Peas	0.54
Okra	0.39
Dill	0.09
Mustard Seed	0.17
Spearmint	0.52
Stone Fruits	0.70
Sugar, Cane & Beet	2.39
Sunflower	0.11
Wheat	0.64
All Foods	76.695[2]

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[1] To estimate exposure to trifluralin containing 1 ppm NDPA these figures would be divided by 5.

[2] Equivalent to 1.92 x 10^{-9} mg/kg body weight/day:

$$\frac{[(76.695 \text{ mg/kg of diet}) (1.5 \text{ kg diet/day})]}{60 \text{ kg}}$$

for this method (0.I ppb). Using this method, the total dietary exposure is 2.3 x 10^{-7} mg/kg body weight/day. This estimate has not been used further in the Agency reviews since it is two orders of magnitude greater than the previously-stated level, which is the maximum level that could be present if all of the NDPA in trifluralin (at 5 ppm contamination) were taken up by plants growing on treated sites.

F. Cancer Risk Assessment

I. Introduction

The Agency's Interim Cancer Assessment Guidelines (Cancer Guidelines) (41 FR 21402) state that when a chemical is judged to be a potential human carcinogen, the Agency will estimate its possible impact on public health at current and anticipated levels of exposure. The Cancer Guidelines also recognize that the available techniques for assessing the magnitude of cancer risk to human populations based on animal data are at best very crude; this is due to uncertainties in the extrapolation of dose-response data to very low dose levels and to differences in levels of susceptibility of animals and humans. Accordingly, these risk estimates are neither scientific certainties nor absolute upper limits on the risk of cancer from use of Treflan. Rather, these estimates should be viewed as a health hazard index that incorporates the degree of carcinogenic activity and human exposure to the compound.

The Agency estimated the risk of cancer to Treflan users in 1977 when it responded to a petition to suspend registrations for this herbicide (42 FR 40009, August 8, 1977). Due to inadequate NDPA field monitoring data, additional assumptions to those normally made in risk estimation were necessary in that analysis. The 1977 estimate is summarized in Table 13.

2. Evaluation of Cancer Data

The Agency's Carcinogen Assessment Group (CAG) has prepared an update of the 1977 estimate of cancer risk from trifluralin (Treflan)/NDPA use. This expanded evaluation (CAG, 1978) was based upon a large volume of data from the published literature, special field monitoring data provided by the registrant, and contact with various experts knowledgeable in relevant scientific disciplines. These studies are discussed in the following sections.

a. Trifluralin

Three lifetime rodent feeding studies assessed the carcinogenicity of trifluralin. Two were performed by the registrant (Worth et al., 1966), and one was conducted by Hazelton Laboratories America, Inc. under the sponsorship of the National Cancer Institute (NCI, 1978).

TABLE 13

CARCINOGENIC RISK TO AGRICULTURAL WORKERS FROM A TWO-YEAR PERIOD OF EXPOSURE TO NDPA[1/]

Category	Risk 1-Hit Model	 Log-Probit Model
Applicators		
Individual Risk	2.0×10^{-7}	4.5×10^{-12}
Number of Cancer Cases	9.6×10^{-2}	2.0×10^{-6}
Field Workers		
Individual Risk	7.1×10^{-8}	9.0×10^{-16}
Number of Cancer Cases	2.7×10^{-3}	3.0×10^{-11}

1/ Treflan was assumed to contain 16 ppm NDPA for this analysis.

(1) Rat Study R31-61 (Worth et al., 1966)

In this study, male and female Harlan-Wistar rats were fed trifluralin for two years. Out of the initial six animals of each sex in each dose group, the proportion of animals surviving was 1/12 of controls, and 6/12, 4/12, 2/12, and 0/12 in animals dosed with 20, 200, 2,000, and 20,000 ppm trifluralin, respectively. The animals in the highest dose group were much smaller and died at a much earlier age than the animals given other doses. According to an FDA review (Schultz, 1967), the difference in ages at death was statistically significant. A variety of pathological conditions were observed, but too few of the animals survived to draw meaningful conclusions. The CAG concluded that this study showed no evidence of carcinogenicity, but that the study was not an adequate basis for safety evaluation because of the low number of animals in each test group and the low number of animals surviving (CAG, 1978).

(2) Rat Study R0283 (Worth et al., 1966)

Worth et al. (1966) fed male and female Cox rats doses of 0, 200, 1,000, and 2,000 ppm trifluralin for two years. He used 25 animals of each sex per dose group. There were no significant differences between dose groups in the number of survivors, food consumption, weight gain, hematocrit, hemoglobin, red blood cell counts, glucose, or serum glutamic pyruvic transaminase (SGPT) determinations.

The number of survivors in each group ranged from 9 to 13 of the initial 25, except for the group of 1,000 ppm males, from which only three survived. In the pathological diagnosis, the only treatment-related effects observed were: an increase in pheochromocytomas of the adrenal medulla in males of the two high dose groups; an increase in "light cell" adenomas and carcinomas of the thyroid in the males of the two highest dose groups; and a higher rate of progressive glomerulonephrosis in all treated males than in controls. Since only the latter effect was statistically significant, the CAG concluded that this study showed no evidence of carcinogenicity and that the study was an adequate basis for safety evaluation. Schultz (1967), in his review of this study for FDA, concluded that thyroid and kidney lesions indicated a possible chronic endocrine system abnormality.

(3) NCI Bioassay (NCI, 1978)

In this study, trifluralin was fed to Osborne-Mendel rats for 78 weeks; the animals were observed for an additional 33 weeks and then sacrificed. The same preparation was administered to B6C3F1 mice for 78 weeks, and the animals were observed for 12 additional weeks and then sacrificed.

The technical grade trifluralin used in this study was characterized at the beginning of the bioassay by melting point range determination and gas-liquid chromatography. The material had a wide melting-point spread (6°C), indicating that more impurities were present than company specifications indicated. The chromatographs showed 13 minor peaks and indicated a purity of greater than 90%. Results of a second analytical characterization done one year later showed no significant sample decomposition. Three years later (after the completion of the bioassay), NDPA was found in the test material at a concentration of 84 to 88 ppm.

The rats initially received doses of 13,000 and 6,500 ppm trifluralin. In week 22 the doses were reduced to 6,500 and 3,250 ppm because of toxic signs. Then in week 63, high dose females were fed no trifluralin for a week, then fed 6,500 ppm for four weeks. This cyclic pattern of one week off and four weeks on was continued for the rest of the treatment period. In the high-dose male rats the cyclic feeding procedure was started at week 68 of the experiment. The low dose males and females, however, received a constant dose. Table 13 gives the time-weighted average doses of trifluralin and NDPA fed to the rats.

The initial trifluralin concentrations for male mice were 4,000 and 2,000 ppm; for female mice they were 9,000 and 4,500 ppm. In week 18 the female doses were reduced to 4,500 and 2,250 ppm, and in week 57 the compound was withdrawn from the high dose group of both sexes. The cyclic pattern described for the rats of one week off and four weeks on the compound was continued for the mice until week 78.

The time-weighted average doses of trifluralin and NDPA fed to the mice are tabulated in Table 14, along with the lifetime averages. The lifetime of the experiment was the feeding plus observation time, which was 90 weeks for mice and 111 weeks for rats. During the course of this bioassay several pathology protocols were in effect, each for different periods of time. In addition, the number of animals for which particular organs, tissues, or lesions were examined microscopically varied and does not necessarily represent the number of animals that were placed on experiment in each group.[7]

At the dose levels used in this experiment, the results are inadequate to demonstrate that trifluralin is a carcinogen in Osborne-Mendel rats (NCI, 1978). The survival of the rats was adequate, since over 46% of the rats survived in all groups and treated groups did not differ significantly from controls. The body weight was uniformly lower in treated groups than controls, and clinical symptoms of aging were observed in all groups. The histopathological findings were typical of aging rats, with no significant differences between treated and control groups.

However, in female B6C3F1 mice, trifluralin was associated with a statistically significant increase in

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[7] The Agency's Carcinogen Assessment Group (CAG) considers these variations to be inconsequential in the final analysis, since they are adequately accounted for in the tabulated data.

TABLE 14

TIME-WEIGHTED AND LIFETIME AVERAGE DOSES OF TRIFLURALIN AND NDPA (ppm) (NCI, 1978)

Species	Dose Group	Time-Weighted Average Trifluralin	Time-Weighted Average NDPA[2]	Lifetime Average[1] Trifluralin	Lifetime Average[1] NDPA
Male Rats	High	8,000	.688	5,622	.483
	Low	4,125	.355	2,899	.249
Female Rats	High	7,917	.681	5,563	.479
	Low	4,125	.355	2,899	.249
Male Mice	High	3,744	.322	3,245	.279
	Low	2,000	.172	1,733	.149
Female Mice	High	5,192	.447	5,000	.387
	Low	2,740	.236	2,375	.205

1/ Average over the duration of dosing and observation. The conversion factor for rats is 78/(78+83) and for mice 78/(78+12).

2/ NDPA is assumed to be present at 86 ppm in the technical trifluralin.

hepatocellular carcinomas and alveolar/bronchiolar adenomas under conditions of this experiment (NCI, 1978). Table 15 presents the data on which these conclusions were based. Although the incidence of squamous cell carcinomas of the stomach was not statistically significant compared to either matched or pooled controls, this tumor type is rarely seen in this strain of mouse. In fact, in none of the 1,985 untreated female (B6C3F1) mice in the NCI bioassay program has a tumor of this type been found. With such a low historical background rate (0/1985), NCI considered even one squamous cell carcinoma of the stomach to be a biologically significant finding. The NCI report concluded that the occurrence of related proliferative lesions of the stomach in treated animals provided supplementary evidence that these tumors were related to the trifluralin treatment. NCI found no significant differences between treated male mice and either pooled or matched controls.

The survival patterns were also different for males and females. The males of both dose groups and the control group died earlier in the bioassay than did the females; the male survival rate for all groups was about 40%. In females the control and low dose survival rate stayed above 90% even at 90 weeks, whereas in the high dose group the 60% survival point was at 86 weeks (compared to 63 weeks for high dose males). Since in the last 10 weeks mortality in high-dose females was accelerated more than in the other groups, fewer were at risk from late-developing tumors; therefore, the incidence of tumors in the females of the high dose group might be underestimated. NCI did not estimate the magnitude of this effect.

TABLE 15

INCIDENCE OF SIGNIFICANT TUMORS IN FEMALE MICE FED TRIFLURALIN (NCI,1978)

Lifetime Average Doses (ppm)		Hepatocellular Carcinomas	Lung: Alveolar/Bronchiolar Adenoma	Stomach: Squamous Cell Carcinoma
Trifluralin	NDPA			
0	0	0/60 (pooled)	0/59 (pooled)	0/60 (pooled)
0	0	0/20 (matched)	0/19 (matched)	0/20 (matched)
2,375	0.205	12/47 (26%)	6/43 (14%)	4/45 (9%)
5,000	0.387	21/44 (48%)	3/30 (10%)	1/44 (2%)

(4) Summary of Trifluralin Carcinogenesis Studies

The chronic rat studies submitted in 1966 by the registrant contained no evidence of carcinogenesis at doses up to 20,000 ppm. However, the NCI bioassay demonstrated a significant increase of hepatocellular carcinoma and alveolar/bronchiolar adenomas in female mice fed trifluralin at 2,375 and 5,000 ppm. Trifluralin induced no detectable carcinogenic response in male mice or in rats of either sex. The irregularity of the NCI dosing schedule and the variation in pathology protocols do not invalidate the results of this test, but the positive response in female mice could have been caused by the high levels of NDPA found in the trifluralin used in the study. This possibility is discussed further in the following section.

b. NDPA

(1) Method

Four rodent lifetime studies on the carcinogenic effects of NDPA have been published: two concerning rats, one hamsters, and one mice. NDPA induced a carcinogenic response in all four studies. In order to evaluate the possibility that the carcinogenic response observed in the NCI bioassay was due to contamination by NDPA, the Agency has reviewed the organs affected in each study and quantified the potency of the compound in inducing the effect.

To quantify the potency, the Agency evaluated the slope B of the one-hit dose-response model:

$$I = 1 - \exp(-Bdt^{m}) \qquad (1)$$

where:

$\underline{I}$ = Tumor incidence after correction for the control incidence with Abbott's correction factor[8],

$\underline{t}$ = Time during the experiment when the incidence I was measured (expressed in fractions of a lifetime)

$\underline{d}$ = Lifetime average daily dose (expressed as ppm equivalent dietary concentration)

$\underline{m}$ = A constant to be determined from the data[9]

When the dose d is expressed in these units, it can be assumed that the potency factor B is applicable to all species. This is equivalent to assuming that the tumor induction time in days is proportional to the animal's life span, and that the carcinogenic efficacy of administering the compound at a certain dose rate (in mg/day) is proportional to the animal's rate of calorie, food, or oxygen consumption.

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[8] The factor is $I = (p_t - p_c)/(1 - p_c)$ where p_t is the proportion of treated animals with tumors and P_c is the proportion of control animals with tumors.

[9] This value is assumed to be 3.0 when no data are available in the experiment.

(2) Druckery et al., 1967a

Druckery et al. (1967a) administered NDPA in the daily diet to B-D rats at dose levels of 4, 8, 15, and 30 mg/kg/day for the lifetime of the animals. No differences were observed between males and females. At 30 mg/kg/day, all 15 rats had liver cancer. At 15 mg/ kg/day, all 15 had liver cancer, and one had esophageal cancer as well. At 8 mg/kg/day, 15 of the 16 had liver cancer, and four also had carcinomas of the esophagus and pharynx. At 4 mg/kg/day, 12 of 14 had liver cancer, six had carcinomas at the base of the tongue, and an unspecified number of others had esophageal cancer. The average induction time for the tumors (organ not specified but probably liver tumors) was 120, 155, 202, and 300 days for the dose groups of 30, 15, 8, and 4 mg/kg/day, respectively. Using a series of equations described in detail in the Agency's cancer risk assessment of trifluralin (CAG, 1978), the Agency calculated the potency of NDPA to be 0.0733 in Druckery's rat experiment.

(3) Reznik et al., 1975

Reznik et al. (1975) administered NDPA subcutaneously to Sprague-Dawley rats once per week at doses of 0, 24.36, 48.72, and 97.44 mg/kg/week for life. The surviving controls were sacrificed 100 weeks after the start of the experiment; all 10 rats in each treatment group died by week 71.

All animals were autopsied and histologically examined. The data, presented in Table 16, show that, with the exception of lung tumors in females, both males and females had a statistically significant higher incidence of tumors of the nasal cavity, lung, esophagus, and liver than controls ($p < .05$ with no correction for multiple comparisons). The highest incidence occurred in the nasal cavity and the liver. The potency of NDPA in this experiment was 0.0763.

(4) Pour et al., 1973

Pour et al. (1973) demonstrated the marked carcinogenic effect of NDPA in Syrian golden hamsters. In this study Pour et al. administered NDPA subcutaneously once per week to hamsters at doses of 3.75, 7.5, 15, 30, and 60 mg/kg/week. A control group was used in these experiments, but no data were given for it. Initially 40 animals (20 females and 20 males) were started in each group. The experiment was terminated after the death of the last treated animal, and complete necropsies were performed on all animals except those lost through cannibalism. Table 17 shows the findings, which are not broken down by sex, since both sexes responded in the same way.

TABLE 16

INCIDENCE OF TUMORS IN SPRAGUE-DAWLEY RATS FROM NDPA
(Reznik et al., 1975)

				Nasal Tumors				
Sex	Dose (ppm) 1/	Average Survival Time (wks) 2/	TBA 3/	M,N,MS 4/,5/	Endoturbinals	Lungs	Esophagus	Liver
Male	278	24.8	8	7/10 p=.00042	1/10 p=.33	4/10 p=.0077	1/10 p=.33	5/10 p=.0018
	139	26.9	6	5/10 p=.0088	0/10	3/10 p=.030	5/10 p=.0018	0/10
	70	39.8	8	7/10 p=.00042	3/10 p=.030	0/10	1/10 p=.33	0/10
	0	78.0	2	1/20	0/20	0/20	0/20	0/20
Female	278	27.8	8	4/10 p=.031	1/10 p=.33	2/10 p=.103	1/10 p=.33	6/10 p=.00035
	139	35.0	8	7/10 p=.00042	6/10 p=.00035	1/10 p=.33	0/10	2/10 p=.103
	70	38.2	7	5/8 p=.0030	2/8 p=.074	1/8 p=.29	3/8 p=.017	0/8
	0	85.5	5	1/20	0/20	0/20	0/20	0/20

1/ Doses are calculated as ppm dietary equivalent assuming rats eat 5% of their body weight/day. For example, the highest dose is 97.44 mg/kg/week x 1/7 x 1/.05 = 278 ppm.
2/ Average survival time was not given separately for males and females.
3/ Number of tumor-bearing animals. 4/ M = maxilloturbinals, N = nasoturbinals, MS = maxillary sinuses.
5/ Results of Fisher's exact test for the significance of the differences in proportions between treated and control groups are designated as p values.

TABLE 17

INCIDENCE OF TUMORS IN SYRIAN GOLDEN HAMSTERS FROM NDPA
(Pour et al., 1973)

Dose 1/ (ppm)	Effective Number Of Animals	Average Survival Time (wks)	Nasal and Paranasal Tumors		Laryngobronchial Tumors		Lung Tumors	
			Incidence	Latency/2/ Lifetime	Incidence	Latency/ Lifetime	Incidence	Latency/ Lifetime
6.7	32	54	22/32 =.69	38/85 =.45	21/32 =.66	38/85 =.45	5/32 =.16	42/85 =.49
13.4	40	49	22/40 =.55	26/85 =.31	32/40 =.80	28/85 =.33	8/40 =.20	46/85 =.54
26.8	36	40	30/36 =.83	26/85 =.31	34/36 =.94	24/85 =.28	6/36 =.17	28/85 =.33
53.6	40	33	26/40 =.65	16/85 =.19	39/40 =.98	16/85 =.19	12/40 =.30	28/85 =.33
107.1	37	29	34/37 =.92	24/85 =.28	37/37 =1.0	17/85 =.20	25/37 =.68	24/85 =.28

1/ Doses are calculated as ppm dietary equivalent assuming hamsters eat 8% of their body weight/day as follows (1/7)(1/.08) (dose in mg/kg).

2/ Lifetime was assumed to be 85 weeks in the absence of data on controls. This is between the standard lifetime of mice (78 weeks) and rats (104 weeks).

In the nasal and paranasal cavities, Pour observed benign tumors, squamous cell carcinomas, and adenocarcinomas. The number of squamous cell carcinomas in all animals increased slightly with dose, but the number of adenocarcinomas was strongly dose-dependent. Tumors were also found in the larynx, trachea, and sternal bronchi. The number of tumors in all three areas was dose-dependent, but the ratio of carcinomas to benign tumors was not given. Pour found adenomas (which were not dose-dependent) as well as carcinomas (which were dose-dependent) in the lung. The potency of NDPA in producing nasal, laryngobronchial, and lung tumors was 0.354, 0.0722, and 0.0884, respectively, in this experiment.

(5) Dickhaus et al., 1977

Dickhaus et al. (1977) administered NDPA subcutaneously once per week to female NMRI mice at dose levels of 138, 69, and 34.5 mg/kg/week. A control group was maintained, and the control animals were sacrificed after the last treated animal had died. Table 18 shows the histopathological findings. Dickhaus observed a high incidence of tumors in the nasal cavity, respiratory tract, lungs, and upper gastrointestinal tract in this experiment. Nasal cavity tumors were squamous cell papillomas and carcinomas.

Significance at the lowest dose occurred both with nasal tumors and a combined group consisting of pharynx, esophagus, and stomach tumors. Although in both cases the

TABLE 18

INCIDENCE OF TUMORS IN FEMALE NMRI MICE FROM NDPA
(Dickhaus et al., 1977)

		Nasal Tumors					
Dose 1/ (ppm)	Average Survival Time (wks)	Nasal & Maxillo 2/ Turbinals	Endo- and Ecto- Turbinals	Larynx Trachea Bronchi	Pharynx Esophagus Stomach	Liver	Lung
152	29	5/12 p=.052	4/12 p=.033	6/12 p=.0040	7/12 p=.0074	4/12 p=.033	2/12
76	36	4/14 p=.16	7/14 p=.0029	6/14 p=.0080	7/14 p=.016	1/14	7/14
38	44	9/14 p=.0022	3/14 p=.110	3/14 p=.11	13/14 $p=4.9\times10^{-6}$	0/14	11/14
0	79	1/14	0/14	0/14	1/14	0/14	10/14

1/ Doses are calculated as ppm dietary equivalent assuming mice eat 13% of their body weight/day. For example, the highest dose is 130 mg/kg/wk x 1/7 x 1/0.13 = 152 ppm.
2/ The p-values are results of Fisher's Exact Test for the significance of the difference in proportions between treated and control groups.

tumor response was considerably less at the two higher doses, this must still be considered an effect of treatment, since the tumor site is known to shift with changes in dose for several nitrosamines, including NDPA (Druckery et al., 1967). The Agency estimated the potency of NDPA in this experiment to be 0.391.

c. Comparison of Trifluralin and NDPA Results

Female mice in the NCI experiment had hepatocellular carcinomas, lung adenomas, and squamous cell carcinomas of the forestomach; however, cancer was not induced in male mice or in rats of either sex. In rats, mice, and hamsters, NDPA caused benign and malignant nasal cavity tumors, upper gastrointestinal tract tumors (tongue, pharynx, esophagus, and forestomach), respiratory tract tumors, and lung tumors. The organs in female mice in which trifluralin treatment induced a carcinogenic response are, therefore, also susceptible to tumor induction by NDPA.

The CAG (1978) evaluated the data summarized above to determine whether NDPA levels in trifluralin were sufficient to cause the responses observed in the female mice in the NCI experiment. The NDPA potencies derived earlier were used together with the estimated NDPA concentrations in the NCI test material to calculate the expected incidence of tumors in rats and mice. The potency for mice was assumed to be the same as in the

Dickhaus et al. (1977) mouse experiment, and the potency for rats was taken to be the geometric mean of potencies in the rat experiments of Druckery et al. (1967), Reznick et al. (1975), and the hamster experiment of Pour et al. (1973). These potencies are B = 0.391 for mice and B = $[(0.0733)\ (0.0763)\ (0.354)\ (0.0722)\ (0.0884)]^{1/5} = 0.105$ for rats[10/]. Using these parameters, the Agency calculated the theoretical tumor incidences in the NCI experiment. These are shown in Table 19.

The observed tumor incidence for female mice in the NCI bioassay was about three times higher than the incidence estimated in Table 19. At face value this would indicate that there was insufficient NDPA in trifluralin to account for the response of the NCI animals. However, several factors indicate that the NDPA concentration in the trifluralin used by NCI may have been higher than that measured three years after completion of the bioassay, and which was the basis of the estimate. FDA analyzed the test material in March 1976, three years after completion of the bioassay, and found 88 ppm NDPA contamination. The test material had been stored in a green glass container, under fluorescent lights at a room temperature of 27°C ± 5° during the test and until the FDA analysis (Powers, 1979). Since NDPA is volatile and photolabile, it is likely that the concentration of this impurity in the

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[10/] For rats the potency from Pour et al. (1973) was calculated separately for each of the tumor types (CAG, 1978). The three separate estimates are used in lieu of the 0.641 potency shown earlier in this Section to calculate this mean potency.

TABLE 19

ESTIMATED AND OBSERVED TUMOR INCIDENCE IN THE NCI TRIFLURALIN TEST DUE TO NDPA CONTAMINATION

Sex Species	NDPA Level (ppm)	NDPA Potency B	Estimated Incidence	Observed Incidence[1/]
Male Rats	.483	.105	.051	< .08
	.249	.105	.026	< .08
Female Rats	.479	.105	.050	< .08
	.249	.105	.026	< .08
Male Mice	.279	.391	.106	< .30
	.149	.391	.058	< .30
Female Mice	.387	.391	.151	.48
	.205	.391	.080	.26

[1/] In experiments where response was insignificant, an upper limit was calculated, via Fisher Exact Test, as the incidence above which the treated group would be significant at the .05 level.

NCI trifluralin sample was higher than 88 ppm during the period when it was administered to the test animals (CAG, 1978).

The Agency concluded that the NDPA contamination of the trifluralin used by NCI explains their findings of hepatocellular carcinoma in female mice. This conclusion is based on three factors: 1) there is a close similarity betwen the types of tumor known to be induced by NDPA and those observed in the NCI trifluralin bioassay; 2) the incidence of tumors in the NCI study was only slightly lower than that predicted from data assuming an NDPA contamination level of 88 ppm; and 3) that NDPA levels in the material tested by NCI were probably higher than 88 ppm measured three years after the test and which was the basis of the estimate.

The primary trifluralin registrant is now performing tests to detect the carcinogenicity of trifluralin in which NDPA contamination has been reduced to undetectable levels. The Agency will evaluate results from this test when it is completed. These results should be available during the first-half of 1980.

10/ For rats the potency from Pour et al. (1973) was calculated separately for each of the tumor types (CAG, 1978). The three separate estimates are used in lieu of the 0.641 potency shown earlier in this Section to calculate this mean potency.

3. Cancer Risk Estimate

a. Application-Related Risk

The Agency based its estimate of human exposure to trifluralin and its NDPA contaminant on field studies using commercial Treflan EC containing NDPA at a level of 3.5 to 6.4 ppm (average of 5 ppm). This estimate was discussed for typical use patterns in Section II, E of this report. The vapor and particulate concentrations of NDPA and trifluralin were measured during field applications of Treflan EC under conditions similar to actual field use. These measurements were used to estimate the average yearly inhalation exposure.

The only information available for estimating the amount of NDPA absorbed across the skin is from a rat dermal absorption study submitted by the registrant (Hanasono et al., 1978). From this experiment, CAG estimated that 22% of the NDPA deposited on the skin is absorbed. The rest is either bound to the skin or escapes into the air. This is a crude approximation of the actual situation because it assumes that steady-state conditions are reached in much less than one hour, and that no long-term storage of NDPA would occur in the skin.

Based upon the rationale discussed in the preceeding Section, the Agency calculated the lifetime risk of cancer to individual farmers who use Treflan assuming that the cancer risk from trifluralin itself is zero. The individual lifetime risk, R, from the NDPA equals Bx, where B is the likely value of the slope parameter for the compound (0.4) and x is the lifetime average daily NDPA intake expressed as ppm in the diet.[11] Using this technique, the number of cases which the Agency estimates to occur from a lifetime exposure to this population is NBx, where N is the number of people exposed (both private farmers spraying Treflan in the fields and farmers who assist commercial spray applicators by incorporating Treflan).

Table 20 shows the individual lifetime risk to applicators and the total number of expected cases. These calculations assume a 40-year working lifetime, a 70-year lifespan, and a diet of 1.94 kg/day; they also assume that the amount of trifluralin absorbed from the skin is 22% of the amount deposited on the skin D, and that the amount absorbed via the lung is 100% of the respiratory intake I. The formulas used were:

$$\begin{aligned}\text{Risk} &= Bx \\ &= 0.4 \times 1/365 \times 40/70 \times 1/1.94 \times 10^{-3} \times \\ &\quad (I + 0.22\ D) \\ &= 3.23 \times 10^{-7} \times (I + 0.22\ D)\end{aligned}$$

$$\text{Number of Cases} = NR$$

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[11] Since the value of B is expressed in units of ppm in the diet, it is necessary to convert the NDPA intake to the same units. For this purpose the daily inhalation and daily dermal intake in milligrams in divided by the daily food consumption (1.94 kg) to obtain the equivalent ppm in the diet.

TABLE 20

RISK ESTIMATES FOR TREFLAN APPLICATORS[2]

Crop	Number of People	Inhalation Exposure, I (ug/year)	Dermal Exposure, D (ug/year)	Lifetime Individual Risk x (10^{-7}) 1/	Lifetime Number of Cases
Soybeans	193,138	0.12	1.33	1.30	0.03
Cotton	63,954	0.11	1.08	1.10	<0.01
Tomatoes	13,490	0.04	0.42	0.43	<0.01
Cole Crops	4,162	0.04	0.50	0.49	<0.01
Beans	23,689	0.07	0.75	0.76	<0.01
Trees and Vines	3,985	0.07	0.75	0.76	<0.01
Hops	51	0.23	2.74	2.70	<0.01
Potatoes	1,800	0.05	0.50	0.52	<0.01
Carrots	657	0.07	0.83	0.82	<0.01
Okra	856	0.02	0.17	0.19	<0.01
Greens	3,259	0.01	0.17	0.15	<0.01
Spanish Peanuts	4,474	0.06	0.59	0.61	<0.01
Celery	166	0.11	1.33	1.30	<0.01
Peppers	2,267	0.02	0.17	0.19	<0.01
Mint	55	0.18	2.16	2.10	<0.01
Dill	16	0.08	0.91	0.91	<0.01
Alfalfa	320	0.07	0.83	0.82	<0.01
Spring Wheat	890	0.34	4.07	4.00	<0.01
Mustard Seed	68	0.12	1.33	1.30	<0.01
Safflower	933	0.27	3.24	3.20	<0.01
Sunflower	5,523	0.13	1.50	1.50	<0.01
Sugar Beets	5,178	0.14	1.66	1.60	<0.01
Sugar Cane	116	0.40	4.65	4.60	<0.01
Cucumbers	3,030	0.01	0.17	0.15	<0.01
Cantaloupes	335	0.03	0.33	0.33	<0.01
Watermelons	2,718	0.02	0.25	0.24	<0.01
Dry Peas	202	0.13	1.41	1.40	<0.01
English Peas	2,776	0.04	0.42	0.43	<0.01
Field Peas	156	0.04	0.42	0.43	<0.01
Commercial Applicators (All Crops)	3,800	0.14	1.74	1.70	<0.01
Total	342,064				<0.04

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[1] Column entry is multiplied by the factor in the column heading; i.e., for cotton the risk is 1.1 x 10^{-7}.

[2] These estimates were based upon exposure to Treflan containing 5 ppm NDPA. With all other factors being equal, NDPA exposure, and the risk therefrom would be directly proportional to the product contamination level. Therefore, these risk estimates can be adjusted by a factor equal to that factor which describes the relation of the contamination level to 5 ppm if one desires to estimate the risk from Treflan contamination level other than 5 ppm.

b. Post-Application Risk

Exposure to workers entering the fields after Treflan has been incorporated into the soil was discussed in Section II,E,2 of this document. Using the method reported by Mittelman (1978), the Agency estimated post-application exposure to NDPA for several crops. The cancer risk from these types of exposure is summarized in Table 21.

The expected number of cancer cases was calculated per 100,000 exposed workers becase an estimate of the number of field workers working in these crops was not available.

Since this model did not consider photodegradation of NDPA, CAG (1978) made a second estimate in order to arrive at a more probable risk estimate for field workers. This estimate, which was discussed in Section II (E) of this document, considered such exposure to be negligible; therefore, the risk would also be negligible.

c. Dietary Risk

Table 22 summarizes the risk of cancer from potential dietary exposure to NDPA, calculated by using the one-hit model for risk assessment. The formulas for calculating the estimates in the table are as follows:

1) Maximum Daily NDPA Intake = $\sum t_i \times a_i \times b_i \times 1/89{,}000$

TABLE 21

POST-APPLICATION RISK ASSOCIATED WITH TRIFLURALIN
(Mittelman's Exposure Method)

Crop	NDPA Exposure/Year (Micrograms)	Lifetime Individual Risk (x 10^{-7})	Lifetime Cases/ 100,000 Field Workers
Beans	0.013	0.042	<0.01
Tomatoes	0.022	0.069	<0.01
Tree and Vine	0.064	0.210	<0.01
Cole Crops	0.026	0.083	<0.01

TABLE 22

ESTIMATE OF MAXIMUM CANCER RISK TO THE GENERAL POPULATION[1/] [2/]

Food Type	Trifluralin Tolerance (mg/kg of diet)	Fraction of Food in Diet	Fraction of Crop Treated	Maximum Daily NDPA Intake, ($x\ 10^{-9}$) mg/kg of Diet	Lifetime Individual Risks ($x\ 10^{-9}$)	Total Number of Cases in Lifetime
Asparagus	0.05	.0014	1.000	0.79	0.315	0.07
Carrots	1.00	.0048	0.403	21.74	8.690	1.91
Citrus Fruit	0.05	.0381	0.079	1.69	0.676	0.15
Corn, grain	0.05	.0100	1.000	5.62	2.250	0.49
Cottonseed	0.05	.0015	0.695	0.59	0.234	0.52
Curcurbits						
Cantaloupe	0.05	.0052	0.100	0.29	0.117	0.03
Cucumber	0.05	.0073	0.291	1.19	0.477	0.11
Watermelon	0.05	.0143	0.300	2.41	0.964	0.21
Fruiting Vegetables						
Peppers	0.05	.0012	0.378	0.26	0.102	0.02
Tomato	0.05	.0287	0.688	11.09	4.440	0.98
Grapes/Raisins	0.05	.0049	0.079	0.22	0.087	0.02
Hops	0.05	.0003	0.251	0.04	0.017	<0.01
Leafy Vegetables						
Broccoli	0.05	.0010	0.650	0.37	0.146	0.03
Brussel Sprouts	0.05	.0003	0.650	0.11	0.044	0.01
Cabbage	0.05	.0074	0.665	2.76	1.106	0.24
Cauliflower	0.05	.0007	0.546	0.22	0.086	0.02
Celery	0.05	.0029	0.394	0.64	0.257	0.06
Collards	0.05	.0008	0.960	0.43	0.173	0.04
Kale	0.05	.0003	0.960	0.16	0.065	0.01
Mustard Greens	0.05	.0006	0.859	0.29	0.116	0.03
Turnip Greens	0.05	.0003	0.963	0.16	0.065	0.01
Mung Beans	2.00	.0003	1.000	6.74	2.697	0.59
Nuts	0.05	.0010	0.079	0.04	0.018	<0.01
Peanuts	0.05	.0036	0.196	0.40	0.159	0.03
Peppermint	2.00	.0003	0.077	0.52	0.208	0.05
Root Crop Vegetables						
Potatoes	0.05	.0543	0.053	1.62	0.647	0.14
Safflower	0.05	.0003	1.000	0.17	0.067	0.01
Seed/Pod Vegetables						
Beans	0.05	.0204	0.756	8.66	3.465	0.76
Soybeans	0.05	.0092	0.377	1.95	0.779	0.17
Peas	0.05	.0069	0.138	0.54	0.214	0.05
Okra	0.05	.0007	1.000	0.39	0.157	0.03
Dill	0.05	.0003	0.536	0.09	0.036	0.01

Mustard Seed	0.05	.0003	1.000	0.17	0.067	0.01
Spearmint	2.00	.0003	0.077	0.52	0.208	0.05
Stone Fruits	0.05	.0125	1.000	0.70	2.809	0.62
Sugar, Cane & Beet	0.05	.0364	0.117	2.39	0.957	0.21
Sunflower	0.05	.0003	0.650	0.11	0.044	0.01
Wheat	0.05	.1036	0.011	0.64	0.256	0.06
All Foods				76.70		<8.00

1/ This table represents a maximum estimate based upon calculated NDPA residue levels. NDPA residues have not been detected in the following crops which have been grown in fields treated for successive years with Treflan: soybeans, mature cottonseed, mature cauliflower (fruit and leaves), mature carrots (roots and tops), volunteer alfalfa, and cotton seedlings test sensitivity 0.1 to 0.2 ppb).

2/ These estimates were based upon exposure to Treflan containing 5 ppm NDPA. With all other factors being equal, NDPA exposure, and the risk therefrom would be directly proportional to the product contamination level. Therefore, these risk estimates can be adjusted by a factor equal to that factor which describes the relation of the contamination level to 5 ppm if one desires to estimate the risk from Treflan contamination level other than 5 ppm.

2) Lifetime Individual Risk = Maximum Daily NPDA Intake x 0.4[12/]

3) Number of Cases in Lifetime = Lifetime Individual Risk x 2.2 x 10^8

for the i th food item, where,

t_i is the food tolerance for trifluralin

a_i is the fraction of the food in the standard diet

b_i is the fraction of the crop treated with Treflan

The values for t_i, a_i, and b_i were reported by Agency health scientists (Beusch and Johnson, 1978).

The risk from dietary exposure is a maximum number based on the assumption that NDPA residues are present. These residues may be much lower. In fact, NDPA residues have not yet been detected in harvestable crops which have been grown in fields treated with Treflan EC.

[12/] 0.4 is a constant calculated earlier for NDPA in this Section of the document.

G. Mutagenesis and Spindle Effects

1. Introduction

40 CFR 162.11(a)(3)(ii)(A) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s)... induces mutagenic effects, as determined by multitiest evidence."

The Agency has concluded that the NDPA contaminant of trifluralin, and therefore products containing trifluralin exceed the multitest criterion for mutagenicity*/ [40 CFR 162.11(a)(3)(ii)(A)] and that a rebuttable presumption against these registrations should be issued. The Agency's evaluation of the data upon which this conclusion was based and its evaluation of the risk from this hazard (Mauer 1978 and 1979) is discussed in the following paragraphs. These data are summarized in Tables 23 and 24.

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*/ The Agency has also compared the existing data on trifluralin and its NDPA contaminant to the mutagenicity testing guidelines contained in its proposed guidelines for human hazard evaluations (43 FR 37336, August 22, 1978). The Agency has concluded that the criterion for mutagenicity contained therein has also been exceeded by products containing trifluralin.

TABLE 23

MUTAGENICITY TESTS OF TRIFLURALIN (PART I) AND NDPA (Part II)

(Part I)

	Technical Trifluralin		
Test System	Species/Strain	Result	Reference
A. Gene Mutations			
1. Bacterial	Salmonella typhimurium (8 Strains)	Neg[3]	Andersen et al., 1972
	Salmonella typhimurium[1,2]		
	TA 100	Neg	Simmon et al., 1977
	TA 1535	Neg	Simmon et al., 1977
	TA 1537	Neg	Simmon et al., 1977
	TA 1538	Neg	Simmon et al., 1977
	Escherichia coli[1,2]		
	WP2	Neg	Simmon et al., 1977
2. Insect	Drosophila melanogaster	Neg[4]	Murnik, 1978a
3. Other	Escherichia coli with T_4 bacteriophage	Neg[3,6]	Andersen et al., 1972
B. Chromosomal Mutations			
1. Insect	Drosophila melanogaster	Neg[4]	Murnik, 1978
C. Primary DNA Damage			
1. DNA Repair, Bacteria	Escherichia coli W3110/p 3478	Neg[1,2]	Simmon et al., 1977
	Bacillus subtilis H17(Rec^+)/M45(Rec^-)	Neg[1,2]	Simmon et al., 1977
2. Yeast Mitotic Recombination and/or Gene Conversion	Saccharomyces cerevisiae D3	Neg[1,2]	Simmon et al., 1977
3. Mammalian Cell Unscheduled DNA Synthesis	Human Fibroblasts WI-38 Cells	Neg[1,2]	Simmon et al., 1977

TABLE 23

MUTAGENICITY TESTS OF TRIFLURALIN (PART I) AND NDPA (Part II)

(Part II)

Test System	NDPA		
	Species/Strain	Result	Reference
A. Gene Mutations			
1. Bacterial	Salmonella typhimurium		
	Unspecified	Pos[5]	McCann et al., 1975
	TA 98	Neg[5]	Yahagi et al., 1977
	TA 100	Pos[5]	Yahagi et al., 1977
	TA 1530	Pos[5]	Bartsch et al., 1976 Camus et al., 1976
	TA 1535	Pos[5]	Olajos and Cornish, 1976
	Escherichia coli		
	Sd-B(TC)	Pos[5]	Nakajima et al., 1974
2. Mammalian Somatic Cells in Culture	Chinese Hamster V79 Lung Cells	Pos[5]	Kuroki et al., 1977
B. Chromosomal Mutations			
1. Mammalian cells in culture	Chinese Hamster CHL cells	Pos[3]	Matsuoka et al., 1979
C. Primary DNA Damage			
1. Yeast Mitotic Recombination and/or Gene Conversion	Saccharomyces cerevisiae D3	Pos[5],	Brusick and Mayer, 1973

1/ Strains tested with and without metabolic activation.
2/ Test material contained 87 ppm NDPA as a contaminant.
3/ No metabolic activation used.
4/ Preliminary data - sample of test material with NDPA removed in the laboratory.
5/ Metabolic activation used.
6/ Test for rII mutation.

TABLE 24

MUTAGENICITY AND RELATED TESTS WITH FORMULATED TREFLAN (PART I) UNSPECIFIED FORMS OF TRIFLURALIN (PART II)

(Part I)

	Treflan Formulations		
Test System	Species/Strain	Result	Reference
A. Gene Mutations			
1. Bacterial	Salmonella typhimurium (8 Strains)	Neg[1]	Andersen et al., 1972
2. Insect	Drosophila melanogaster	Neg[5],[6]	Murnik, 1978
B. Chromosomal Mutations			
1. Insect	Drosophila melanogaster	Pos[5],[6]	Murnik, 1978
2. Other Studies	Exposed Humans	Pos[4]	Yoder et al., 1973
	Neurospora	Pos[5]	Griffiths, 1978
	Sordaria	Pos[5]	Bond, 1978

(Part II)

	Unspecified Forms of Trifluralin		
Test System	Species/Strain	Result	Reference
A. Gene Mutations			
1. Bacterial	Salmonella typhimurium[1]		
	TA 1535	Neg	Shirasu et al., 1976
	TA 1536	Neg	Shirasu et al., 1976
	TA 1537	Neg	Shirasu et al., 1976
	TA 1538	Neg	Shirasu et al., 1976
	Escherichia coli[1]		
	B/r WP2 hcr$^+$	Neg	Shirasu et al., 1976
	WP2 hcr$^-$	Neg	Shirasu et al., 1976
B. Chromosomal Mutations			
1. Plants	Haemanthus katheriniae (Blood lilly)	2/	Jackson and Stetler, 1973
	Tradescantia paludosa	3/	Sawamura and Jackson, 1968
	Vicia faba	3/	Sawamura and Jackson, 1968
2. Salamanders	Triturus helveticus (salamander)	7/	Sentein, 1977
	Pleurodeles waltlii (salamander)	7/	Sentein, 1977

TABLE 24
(Part II Continued)

Test System	Species/Strain	Result	Reference
	Unspecified Form of Trifluralin		
C. Primary DNA Damage			
I. DNA Repair, Bacteria	Bacillus subtilis H17(Rec$^+$)/M45(Rec$^-$)	Neg[1]	Shirasu et al., 1976

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[1] Metabolic activation not used.
[2] Decreased number of microtubules, accumulation of large vessicles at the cell plate region.
[3] Disruption of mitotic process, temporarily impeded chromosome movement.
[4] Chromatid lesions in lymphocytes of workers exposed to many herbicides.
[5] Preliminary data.
[6] Product sample used contained 177 ppm NDPA.
[7] Inhibition of mitosis as a consequence of spindle abnormalities (microtubule and aster formation).

2. NDPA Mutagenicity Data

The principal contaminant of trifluralin technical preparations is NDPA, which is a demonstrated oncogen in rodents (Montesano and Bartsch, 1976). NDPA has been studied in *in vitro* mutagenicity assays with bacteria and yeasts, and in mammalian cell culture, coupled with appropriate mammalian metabolic activation systems (see Table 23). In bacterial assays, NDPA has caused reverse mutations by base-pair substitution at concentrations up to 1.0 millimole (mM), but only in the presence of complete liver enzyme preparations from rodents; when the cofactors for the microsomal mixed function oxidase were omitted, the mutagenic effect was absent. Positive results for gene mutation as well as chromosomal aberrations were also obtained in Chinese hamster lung cell cultures treated with 20 mM NDPA and a rat liver enzyme preparation (Kuroki et al., 1977; Matsuoka et al., 1979).

Kruger (1973) also found direct evidence that NDPA alters genetic material *in vivo*; he reported the presence of alkylated guanine residues in DNA after administering NDPA to rats.

3. Trifluralin Mutagenicity Data

Positive results have not been obtained in tests with technical trifluralin containing known and undetermined levels of NDPA contamination in a number of mutagenicity systems. Tests resulting in negative responses are discussed below.

a. Bacterial Tests

Simmon et al. (1977) tested 20 pesticides, including technical trifluralin (90%) containing 87 ppm NDPA (as a contaminant), in reversion-type mutagenic assays. Four *typhimurium* strains and the WP-2 strain of *Escherichia coli* were used, both with and without mammalian metabolic activation systems. Activation was obtained by using liver preparations from rats pre-treated with the polychlorinated biphenyl (PCB), and Arochlor 1254. Trifluralin was negative in this study.

Simmon et al. (1977) also tested the same trifluralin sample for unscheduled DNA synthesis in human fibroblasts (WI-38 cells), mitotic recombination in the yeast *Saccharomyces cerevisiae* strain D3, and preferential toxicity in repair-deficient strains of *Escherichia coli* and *Bacillus subtilis* as compared to strains which could repair DNA damage. Each of these assays was performed both with and without mammalian metabolic activation, and over a wide range of trifluralin concentrations. Trifluralin was negative in all of these assays. The Agency considers the experimental and data reporting procedures used in this study to be adequate (Sandhu, 1977).

Andersen et al. (1972) evaluated 109 herbicides, including both technical and formulated (44.5%) trifluralin. Specifically, they looked for induction of point mutations in a battery of standard bacterial and viral plate assays involving base-pair substitution and frameshift reversions, as well as forward mutation. Results were compared to positive results with known mutagens specific for each of four assays; single doses of all test chemicals, including formulated trifluralin (20 or 25 ug per plate) did not induce any changes significantly different from the spontaneous rates of mutation in eight histidine-requiring mutants of Salmonella typhimurium, two rII mutants of bacteriophage T_4, or Escherichia coli strain KB.

The Agency considers this study to be inconclusive in demonstrating safety, because no exogenous metabolic activation was provided to mimic possible conversion of the chemical to potentially active intermediates, and only one dose was administered (Mauer, 1978; Sandhu, 1977).

Shirasu et al. (1976) studied the mutagenicity of an unspecified form of trifluralin in four histidine-requiring strains of Salmonella typhimurium in a standard Ames assay, as well as in differential toxicity assays with Bacillus subtilis strains H17 (Rec^+) and M45 (Rec^-), and in reversion assays using two strains of Escherichia coli which require tryptophan. For each of these assays, bacterial cultures were treated with a single saturated paper disc containing 0.02 ml solution of a standard sample made up at a concentration of 1 mg trifluralin/ml dimethylsulfoxide.

Trifluralin was negative for mutagenicity in this study, but since mammalian metabolic activation was not used, and only one concentration was tested, the Agency regards these results as inconclusive (Sandhu, 1977).

b. Insect Studies

Preliminary results from a study of both gene and chromosomal effects in *Drosophila melanogaster*, (Murnik, 1978 and 1978a) showed "no evidence ... that trifluralin induces point mutations in *Drosophila*," but some of the results of these two separate studies are contradictory.

In one portion of the first study, larvae were fed a diet containing 0.01% formulated trifluralin (44.5% AI) throughout their stages, and the number of sex-linked lethals was recorded in the F_2 (second) generation; in replicate tests, no significant differences were found in percent lethals between the treated (0.10% for the first test) and combined control (untreated spontaneous, 0.12%) groups. No positive controls were reported, and the formulated trifluralin tested contained about 177 ppm NDPA (Bontoyan, 1978). In the second portion, feeding adult males 0.02% of the formulated trifluralin for two days likewise resulted in no increase in sex-linked lethals.

A later repeat of this study with technical trifluralin which contained no detectable NDPA was also negative for sex-linked lethals (Murnik 1978a).

Although preliminary results from the two studies showed no evidence that trifluralin induces point mutations in Drosophila, Murnik reported an increase in chromosomal nondisjunction. Her first study involved the chronic feeding of 0.01% trifluralin (formulated) throughout the larval stages. This resulted in a significant increase (0.12%) of XXY males compared to those of a control population (0.04%). However, the feeding of 0.02% trifluralin (formulated) to adult male Drosophila for two days resulted in no increase in non-disjunction. XXY non-disjunction was the only chromosomal effect reported in this test; there were no increases over controls in chromosome loss (XO progeny) or breakage. When the chromosomal portion of the first study was repeated using technical trifluralin with no detectable NDPA, non-disjunction was not observed in test animals at a level significantly different from that of the control population. Thus these cytogenetic results are inconclusive, as well as contradictory (Chaisson, 1978).

c. Studies with Fungi

Trifluralin has also been tested for non-disjunction in Neurospora crassa (Griffiths, 1978), as well as in Sordaria brevicollis (Bond, 1979). The Agency recently received a tabulation of raw data from Griffiths which indicated increased incidences of "aneuploid" ascospores in treatment groups over a range of concentrations from 1 to 122 mg/l as compared to controls (rate unspecified), but which showed no clear dose-response effect. The preparation used was reported to be a "formulation", but no other details, such as the NDPA level, were given. Hence these results as well as, data from Bond are inconclusive because inadequate information is available to indicate whether a test protocol acceptable to the Agency was followed.

d. Human Survey

Yoder et al. (1973) observed chromosome alterations in lymphocyte cultures prepared from pesticide applicators. Blood was drawn once during the mid-winter lull in spraying operations and again during the peak summer spraying period. Forty-two white male applicators with from 1 to 25 years (mean exposure, 8.5 years) of prior occupational exposure to a variety of pesticides were matched as closely as possible in age and physical characteristics to a control group of 16 businessmen, students, and teachers with no history of involvement with pesticides. The exposed group was further divided into two subgroups. One consisted of 16 people who had been exposed to a variety of 17 insecticides, while the other consisted on 26 employees of weed control agencies who had been exposed to a variety of 14 herbicides (most frequently 2,4-D, amitrole, and atrazine, but also formulated trifluralin). The incidence of chromatid lesions per person in the applicator groups increased significantly over that in the control group, but only in blood samples taken in the summer. Although Yoder et al. observed no heteroploidy (which may be indicative of non-disjunction) in any of the exposed or control cells, they noted a small number of chromatid exchange figures among the exposed groups. The Agency regards this study as inconclusive in implicating trifluralin as a chromosome breaker, since this substance was only one of many pesticides used by the same workers (Mauer, 1978).

e. Plant Studies

The Agency reviewed a number of plant studies in order to determine whether trifluralin has the potential to disrupt the cellular spindle apparatus. These studies were not performed specifically to assess the issue of mutagenicity. In an *in vitro* and ultrastructural study in cellwall free endosperm cells of the African blood lily (*Haemanthus katherinae*), Jackson and Stetler (1973) reported that concentrations of trifluralin, ranging from 0.1 through 100 ppb, inhibited the rate at which cells progressed through all stages of mitosis from prophase to cell plate appearance. Jackson and Stetler observed these effects by time-lapse phase microscopy during a two-hour period. Since 0.1 ppb had a near-maximum inhibitory effect, the data presented from all concentrations were pooled. Electron microscopic studies showed a decreased number of microtubules and an accumulation of large vesicles in the cell plate region.

While the ultrastructural and mitotic index studies appear to have been conducted according to established protocols, the bioassay used to assess these effects is not well documented. Further, Jackson and Stetler established no dose-response relationship included no positive control in the study, used no mammalian metabolic activation with the bioassay, and provided no information on the amount of NDPA which contaminated the study material. This study does indicate, however, that trifluralin interferes with the formation and function of plant cell microtubules, and it may have a potential, therefore, for disrupting the mitotic spindle and thereby inducing numerical chromosomal aberrations (Sandhu, 1977).

Sawamura and Jackson (1968) treated staminal hair cells of the tetraploid, Tradescantia paludosa, and leaf cells of Vicia faba with 0.2 to 1.6 ppb trifluralin. The degree of NDPA contamination was not known for this material. At the highest dose (1.6 ppb), the authors reported the appearance of "dicentric bridges" in late stages of mitosis (anaphase and telophase) in both cell types and cell elongation in staminal hair cells only. This study demonstrates that trifluralin can disrupt various stages of plant cell mitosis; however, it is of limited value since the system is questionable, the data are not quantitative, and the study was not designed to assess mutagenicity (Sandhu, 1977).

f. Salamander Study

Sentein (1977) reported that trifluralin inhibited mitosis by interfering with the spindle apparatus in two urodele salamanders, *Triturus helveticus* and *Pleurodeles waltlii*. Eggs of these species were incubated in various concentrations (1/8 through full saturation) of an unspecified form of "trifluralin" for one to ten mitotic cycles prior to the beginning of cleavage, or at the 2-, 4-, 8-, and 16-blastomere stages. Cytological observations were made during treatment and after various periods of incubation following transfer of eggs to trifluralin-free culture medium. At similar concentrations, the effects reported were more severe in *Pleurodeles* than in *Triturus* eggs, but multinucleate blastomeres and disorganized mitotic figures occurred in both species. Sentein also reported disturbances in chromosomal condensation, especially at chromosomal sites associated with the mitotic spindle attachments, and gaps (discontinuities) at prophase. According to the author, the cytological effects of trifluralin resembled those induced by classic anti-mitotic agents, but trifluralin was much less potent. The author concluded that these effects demonstrate trifluralin interferes with the formation or function of cellular microtubular elements.

This study is difficult to interpret because some details of protocol were not given. For example, the source and composition of the trifluralin were not stated, nor were any control data (the solvent was reported to be polyethylene glycol) included. The study, however, confirms in an animal cytological test system the potential anti-mitotic action of trifluralin previously found in plant cytological studies.

The cytological studies also support the genetic studies in Neurospora and Drosophila which indicate possible non-disjunctional activity of trifluralin (Mauer, 1978).

4. Trifluralin Derivatives

The Agency has also considered the mutagenic potential of degradation and/or metabolic products of trifluralin. Section 162.3(e) defines a degradation product as "...a substance resulting from the transformation of a pesticide by physicochemical or biochemical means." Evidence indicates that trifluralin might be degraded to a series of products, including substituted benzimidazoles in a mammalian-derived *in vitro* microsome system (Nelson et al., 1977). Such conversion has been reported to occur under ultraviolet photodecomposition conditions, especially in the vapor phase above treated soil, as well as in the soil. This is of concern because some benzimidazoles have been shown to be mutagenic (Seiler, 1972).

A recent preliminary report presents some interim results from bacterial mutagenicity assays performed with nine trifluralin metabolites, including the benzimidazoles previously identified (Nelson, 1977), by plate incorporation at concentrations up to 200 ug per plate using a standard battery of five Ames test strains of S. typhimurium, both with and without metabolic activation (Nelson, 1978a, unpublished). In a summary of these results, Nelson reported that he had found "no potent mutagens among these trifluralin derivatives tested thus far", compared to the expected response of positive controls appropriate to each of the test strains. The Agency's inspection of Nelson's tabulations revealed no significant differences between experimental and control groups (Mauer, 1979).

5. Mutagenic Risk Assessment

Neither technical nor formulated trifluralin (containing NDPA at levels up to 177 ppm) have shown any mutagenic activity. The principle contaminant of both (NDPA) has induced mutations in various test systems at concentrations greater than 20 times those contained in current formulations of trifluralin (< 1.0 ppm Mauer, 1978). NDPA is therefore considered to be a mutagen, and the Agency has evaluated the potential for mutagenic risk associated with NDPA contaminated trifluralin.

Two situations of potential mutagenic risk were considered: The direct DNA/gene effects related to the NDPA contaminant; and potential effects to the spindle apparatus induced by trifluralin.

a. DNA/Gene Effects

When tests were performed with metabolic activation, technical-grade trifluralin (containing about 87 ppm NDPA) was negative for gene mutations and primary DNA damage. Formulated trifluralin (as Treflan or unspecified) was also negative in some of the same tests; however, the Agency considered results of these latter tests to be inconclusive since they were performed without metabolic activation. Other preliminary studies indicate that Treflan containing 177 ppm NDPA, as well as trifluralin with no detectable NDPA, give negative results in the *Drosophila* sex-linked recessive lethal test. On the other hand, NDPA by itself has been shown to be mutagenic in several *in vitro* microbial test systems by causing base-pair substitution and primary DNA damage (Chaisson and Burkhalter, 1978). This seeming contradiction may be due to the fact that the NDPA concentrations in the trifluralin preparations tested were too low to produce gene mutations or direct DNA interaction, especially in the presence of trifluralin (Chaisson and Burkhalter, 1978).

Trifluralin/NDPA mutagenesis data are not adequate to determine, much less quantify, any risk for gene or DNA interactions posed by Trifluralin. For the reasons developed below, however, the Agency considers that such a risk would be low, if in fact it exists.

This assessment considers any potential DNA/gene effects to be associated with the NDPA contaminant of trifluralin formulations. To pose a potential, heritable genetic risk to humans, a chemical must be a mutagen and must be capable of reaching mammalian germ cells in a metabolically active form. There is no evidence regarding whether mutagenically active forms of trifluralin or NDPA do or do not reach mammalian germinal tissue, or whether these compounds are metabolized *in situ* to active forms if they do reach these tissues. The NDPA data presented in Table 23 indicate the need for metabolic activation of this compound before it can induce mutagenic responses in test organisms. Although NDPA shows mutagenic activity in some *in vitro* test systems, including mammalian cells in culture, no *in vivo* tests have been performed. To bridge these data gaps, the Agency used information on the structurally related aliphatic nitrosamines, dimethylnitrosamine (DMN), and diethylnitrosamine (DEN).

DMN and DEN are mutagenic in both the Ames and *Drosophila* sex-linked lethal tests. Three mouse dominant lethal studies on these chemicals were also surveyed. A single intraperitoneal dose of DEN (13.5 mg/kg body weight) did not significantly increase mutations in the offspring of treated males (Propping et al., 1972). DMN was also negative when male mice were dosed by the same route with 8 or 9 mg/kg body weight (Epstein et al., 1972). DMN was reported as producing a weak dominant lethal effect in a second study with male mice (Propping et al., 1972). It is of interest that the second study was positive at a DMN dosage lower than that yielding a negative response in the other study; however, the mouse strain and route of administration differed in the two studies. There was only a single drug-treatment group in the Propping et al. study; the lack of varying treatment levels precluded any within-experiment repetition of the results or knowledge of dose-response relationships. The authors did state that the 4.4 mg/kg dose was the highest dosage of DMN compatible with survival. Due to the great variation in the responses of animals in the dominant lethal test and the finding of this positive at a level of significance just meeting the authors' accepted critical level, one is not absolutely certain about the outcome of the test. At face value it suggests that DMN can reach the mammalian gonad. A negative interpretation, however, is consistent with the finding that neither DMN nor DEN stimulated unscheduled DNA synthesis in the mouse testis following intraperitoneal dosing of the test compounds and tritiated thymidine (Gary Sega, 1979, personal communication). Also, DEN was negative in a mouse specific locus test (Russel, 1977). NDPA itself has not been tested for germinal or in vivo mammalian mutations.

Therefore, the Agency considers it unlikely that Treflan containing NDPA would cause a significant risk with respect to DNA and gene effects because:

1. NDPA appears to have point mutagenic activity in some in vitro systems, but information is lacking from in vivo tests. Some other short-chain alkylnitrosamines have been reported to be positive in the Drosophila sex-linked recessive lethal test.

2. There is no direct evidence regarding whether NDPA does or does not reach the mammalian gonad in a genetically active form. As for other nitrosamines, it has been reported that neither DMN nor DEN stimulates unscheduled DNA synthesis in the mouse testis; and only one of three dominant lethal studies with these chemicals in mice suggests a positive effect, and that is a very weak positive with DMN. Additionally, DEN was negative in an inadequate mouse specific locus test.

3. Testing of trifluralin products containing 87 ppm NDPA have been consistently negative for mutagenic and DNA-damaging activity.

4. A preliminary study with Treflan containing 177 ppm NDPA was negative in the Drosophila sex-linked recessive lethal test.

5. The Agency expects human exposure to NDPA through the use of trifluralin to be very low (See Table 6, p. 36).

At this time the Agency is not able to quantify the mutagenic hazard which might be associated with the use of NDPA contaminated trifluralin because information on the presence of the active compound in the mammalian gonad and the results of germinal testing are lacking. The occupational exposure to NDPA (<5.05 ug/year) and those to the general population through consumption of treated food (about 1.92×10^{-9} mg/kg body weight/day assuming the presence of a residue and a 5 ppm level of NDPA contamination in Treflan) is very low.

Since risks of adverse effects are intimately related to exposure and since the expected human exposures to NDPA are low, it is expected that any risk from point mutagenic effects would be low.

Since the exposure estimate above assumed 5 ppm NDPA contamination of trifluralin and since the manufacturer has already lowered the contamination to 1 ppm or less any risk would be reduced further by a factor of about five.

In order to be better able to evaluate point mutagenic risks, other tests on NDPA would need to be conducted, including studies assessing the ability of the chemical to reach the mammalian gonad in a metabolically active form.

Once more, the approach employed should not be interpreted as setting Agency policy for future assessments; it is simply a way to use the data at hand and specifically refers only to Treflan, and/or other trifluralin/NDPA formulations. Any more in-depth procedure must await further results of experimentation.

b. Spindle Effects

The limited studies available appear to show that high concentrations of trifluralin (with or without stated levels of NDPA) have the capacity to disrupt formation or function of the spindle apparatus in dividing cells, thereby having the potential to cause abnormal segregation of chromosomes (non-disjunction).

Inconclusive results from tests with formulated trifluralin (containing about 177 ppm NDPA) in *Drosophila* showed non-disjunction. However, when these tests were repeated using technical trifluralin with no detectable NDPA, negative results were obtained. Inconclusive positive results showing effects to the spindle were also reported when formulated trifluralin (NDPA content unknown) was tested on *Neurospora*.

As a result of recent discussions at the National Institute of Environmental Health Sciences Workshop on "Systems to Detect Induction of Aneuploidy by Environmental Mutagens", four model chemicals including trifluralin (the others are para-fluorophenylalanine, colchicine, and methyl-2-benzimidazole carbamate) are now being tested by several laboratories to investigate their effects on the mechanism of spindle function. Reports of these tests are not yet available (Chaisson, December 14, 1978).

The positive chromosomal effects reported in plants and salamanders indicate that trifluralin (or trifluralin plus NDPA) may affect spindle fibers by interfering with microtubule formation or function. No comparable studies in mammalian test systems, however, either _in vitro_ or _in vivo_, are available. Since the apparatus for cell division does not differ significantly between plants and animals, similar spindle effects might be expected to occur in mammals exposed to trifluralin.

Based on the above information, the Agency scrutinized mammalian and fish studies for evidence of mitotic disturbances or abnormalities in treated embryos, and for any other chromosomal, spindle, or cellular effect of trifluralin on developmental processes. Overt manifestations of such effects would include depressed cell formation and maturation, decreased viability of embryos, high resorption rates, or delayed tissue maturation such as slow rates of ossification in newborns. No such effects were noted in any of the reproduction studies with rats and dogs or in a teratogenicity assay in rabbits (these tests have been determined to be unacceptable under current registration procedures (see Section II. H. 1 and 2). Reports of vertebral hypertrophy in treated fish (Couch et al., 1978 preprint) and variations in skeletal development in mice (Beck, 1977) are not evidence of mitotic spindle effects, and do not support a mutagenic effect of trifluralin in mammalian systems. Evaluation of hematological values from chronic toxicity studies also did not elicit any such evidence (Mauer, 1978).

In summary then, several lines of evidence from both the plant and animal kingdoms suggest that trifluralin products, containing known or unknown levels of NDPA, possess the ability to interfere with the cell division spindle. No studies have been carried out on mammalian somatic or germinal cells, but it might be anticipated that mammalian cells would respond in a manner similar to cells of other organisms.

The Agency concluded that the existing data are not adequate to indicate the existence of a significant risk from effects to the cell division spindle at estimated trifluralin or NDPA exposure levels. In addition it is not clear whether trifluralin itself, a metabolite, or a contaminant in this pesticidal preparation is the active component in this regard. Additional studies will be needed to clarify these uncertainties.

c. Summary

The Agency has evaluated the mutagenicity data on trifluralin preparations (including the formulated product) containing NDPA and considers that in the case of direct DNA effects as well as for spindle effects, there is an inadequate data base upon which to evaluate these potential hazards. In regard to the ability of NDPA to induce mutagenic effects, the expected low exposures to this chemical suggests that the degree of hazard, should NDPA be a germinal mutagen, could be low.

H. Other Chronic Effects

Various N-nitroso compounds have been shown to affect the fetus (see Section II, G of this document). For this reason the Agency reviewed a number of studies in which trifluralin (NDPA contamination level unknown) was tested for reproductive, teratogenic, and developmental effects (Bennett, 1978). These studies are discussed below.

1. Reproduction Studies

Worth et al. (1966) reported the results of a three-generation reproduction study in rats treated with trifluralin. In this study weanling rats of the Harlan strain were fed mash containing either 0, 200, or 2,000 ppm trifluralin. The first litters were discarded at weaning. Animals from the second litters whose individual weights approximated the average weight of their respective litters were used to continue the study.

No significant differences in the growth curves were observed for any of the generations. The indices for fertility, gestation, and viability were lower for the second litter of the F_2 generation in the 2,000 ppm group than for controls. The values for these indices for the 2,000 ppm group in the F_3 generation were comparable to the controls; however, the 2,000 ppm group in the F_3 generation consisted of only one animal. The statistical significance of these results can not be determined since an insufficient number of rats were used in this study. However, the Agency concluded at that time that the no-effect level was 200 ppm based upon the data presented.

Because an insufficient number of study animals were used in this test and because the study animals were stressed from severe temperature regulation problems which occurred when the animals were moved to a new location during this test, the Agency has determined that even though the study did not indicate a trigger for reproductive effects, it does not fulfill present regulatory requirements for an acceptable reproduction study and as such constitutes a data gap (Chitlik, 1979).

2. Teratology Studies

In a rabbit teratology study (Worth et al., 1966), trifluralin was administered orally to four groups (eight animals per group) of New Zealand white rabbits from days 8 through 16 of gestation. Dose levels were 225, 450, or 1,000 mg/kg/day. The animals were sacrificed on the 25th day of gestation and the fetuses were delivered by Cesarean section. The weights of both fetuses and mothers were slightly reduced, and the number of stillborn animals increased in all treatment groups. The number of resorption sites also increased at the highest dose (1,000/mg/kg/day). Neither the decrease in weight, the increase in resorptions, nor the increase in still births was statistically significant.

At the lowest dose (225 mg/kg/day) two animals in one litter had underdeveloped hind limbs and hindquarters. Worth did not consider this effect to have been caused by trifluralin since it was observed in only two of six rabbits from one litter at the low-dose level (47 animals total) and was not statistically significant. At 1,000 mg/kg/day, maternal weight gain decreased. While this is not a teratogenic effect, the Agency decided to use 450 mg/kg/day as the "no-effect" level in order to obtain the most conservative estimate of risk. The Agency has determined that even though this study did not indicate a trigger for teratogenic effects, it does not fulfill present regulatory requirements for an acceptable teratology study since an insufficient number of rabbits were used, dosing was carried out for an insufficient interval of time, and dams were sacrificed prematurely (Chitlik, 1979).

3. Other Studies

Couch et al. (1978 preprint) reported consistent vertebral hyperplasia in sheepshead minnows exposed to various levels of trifluralin throughout their early development (zygote to young adult). Histological examinations of sections of 28-day-old fish revealed an extreme semisymmetrical hypertrophy of vertebrae (3 to 20 times normal) in those minnows exposed to 5.5 to 31 ug/l trifluralin. Fish exposed for 51 days to 16.6 ug/l trifluralin had a more pronounced dysplasia of their vertebrae. Vertebral dysplasia was the only bone effect noted.

Serum calcium concentrations significantly increased, but this occurred only in a pooled serum sample from adult fish exposed for six days to trifluralin at 16.6 ug/l.

The noted hyperostosis was the result of the direct effect of trifluralin on the hormonal control of calcium metabolism of young developing fish rather than an effect on the zygote or embryo since extending the exposure time from 28 days to 51 days increased the observed effect. Surviving fish which were examined after 51 days exposure exhibited no further increase in vertebral dysplasia. Apparently the ability of this species of fish to bioaccumulate trifluralin contributes to this syndrome.

Vertebral hyperplasia in fish is not considered to indicate a human health hazard, since chronic feeding studies performed in mammals (a more appropriate indicator system for humans) did not show the effect (Bennett, 1978).

Beck (1977) studied the effects of trifluralin on normally-occuring variations in skeletal development (e.g. extra knobs on the bones or variations in the number of openings in the bone for nerves). Trifluralin was administered to pregnant CD-1 mice via stomach tube at 1.0 g/kg between days 6 and 15 of gestation. Another group received only the corn oil vehicle, and one group was untreated. The litters were born in isolation and examined after birth and at weaning. Beck sacrificed all offspring at 62 ± 2 days and examined them for more than 40 normally-occurring variations. The results indicated that CD-1 mice which had received prenatal treatments of 1.0/kg/day of trifluralin could be differentiated from the control group by the number, magnitude, and spectrum of normally-occurring skeletal variations.

4. Exposure and Related Risk Estimates

a. Dietary Exposure

The Agency calculated safety factors between the NEL and estimated human dietary exposure (Theoretical Maximal Residue Concentration, TMRC) for the reproduction and teratology studies as follows:

Based upon the rat reproduction study:

a. NEL = 200 ppm

b. Equivalent to 10 mg/kg/day (conversion factor 0.05)

c. Human daily dose in 1.5 kg diet (TMRC) = 0.0429 mg/day

- Equivalent to $\frac{0.0429 \text{ mg/day}}{60 \text{ kg}}$ = 0.00072 mg/kg/day
- NEL: Dietary Exposure = $\frac{10.0 \text{ mg/kg/day}}{0.00072 \text{ mg/kg/day}}$ = 13,889:1
- Safety Factor = 13,889

By adding a factor to this calculation which corrects the estimate for the percent of the commodities actually treated with trifluralin, the modified Theoretical Maximal Residue Concentration ($TMRC_{Mod}$) of trifluralin in the daily human diet is estimated to be 0.0102 mg/day. The safety factor between the NEL in the dog chronic feeding study and the $TMRC_{Mod}$ is greater than 58,000. This was calculated as follows:

Human daily dose in 1.5 kg diet ($TMRC_{Mod}$) = 0.0102 mg/day

- Equivalent to = $\frac{0.0102\ mg/day}{60\ kg}$ = 0.00017 mg/kg/day

- NEL: Dietary $Exposure_{Mod}$ = $\frac{10\ mg/kg/day}{0.00017\ mg/kg/day}$ = 58,824:1

- Safety Factor = 58,824

Based upon the rabbit teratology study, the safety factor for dietary exposure would be as follows:

a. Human Daily Dose in 1.5 kg diet (TMRC) = 0.0429 mg/day

- Equivalent to = $\frac{0.0429\ mg/day}{60\ kg}$ = 0.00072 mg/kg/day

- NEL: Exposure Dietary = $\frac{450\ mg/kg/day}{0.00072\ mg/kg/day}$ = 625,000:1

- Safety Factor = 625,000

b. Human Daily Dose in 1.5 kg diet ($TMRC_{Mod}$)[13/] = 0.0102 mg/day

- Equivalnet to = $\frac{0.0102\ mg/day}{60\ kg}$ = 0.00017 mg/kg/day

- NEL: Exposure $Dietary_{Mod}$ = $\frac{450\ mg/kg/day}{0.00017\ mg/kg/day}$ = 2,647,059:1

- Safety Factor = 2,647,059

[13/] TMRC x percent of total crop receiving trifluralin treatment.

Based upon these figures, the current intake of trifluralin on food crops does not pose a hazard to human reproduction (Bennett, 1978).

b. Acceptable Daily Intake (ADI)

In evaluating an application for a new tolerance, the Agency calculates dietary exposure to the population. For trifluralin the Agency has calculated an acceptable daily intake (ADI) of 0.10 mg/kg body weight/day based upon two- and three-year chronic feeding studies in dogs.[14] The lowest no-effect level (NEL) in those tests was 400 ppm. Converting this to mg/kg/day (400 ppm x 0.025) gave a daily dose of 10 mg/kg/day in the dog. The ADI was then calculated, using a safety factor of 100, to be 0.10 mg/kg/day $\left[\frac{(10 \text{ mg/kg/day})}{100}\right]$.

Assuming an average human body weight of 60 kg, the maximum permissible intake (MPI) was calculated as:

$$60 \text{ kg} \times 0.10 \text{ mg/kg/day} = 6.0 \text{ mg/60 kg person/day.}$$

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[14] An ADI has not been established for trifluralin by the FAO/WHO; however, the National Academy of Scienc (NAS) also calculated an ADI of 0.1 mg/kg/day (NAS, 1977).

Based upon existing tolerances, the theoretical maximal residue concentration (TMRC) for trifluralin in the daily human diet is estimated to be 0.0429 mg/day. This estimate assumes that trifluralin residues in treated commodities exist at the level of the tolerance. Based upon this, the TMRC in the daily diet would be about 0.72% of the ADI (Coberly, 1978). The safety factor between the NEL in the dog chronic feeding study and the TMRC is greater than 13,000. This was calculated as follows:

a. NEL = 400 ppm

b. Equivalent to 10 mg/kg/day (conversion factor 0.025)

c. Human daily dose in 1.5 kg diet (TMRC) = 0.0429 mg/day

- Equivalent to $\frac{0.0429 \text{ mg/day}}{60 \text{ kg}} = 0.00072$ mg/kg/day
- NEL: Dietary Exposure = $\frac{10.0 \text{ mg/kg/day}}{0.00072 \text{ mg/kg/day}} = 13{,}889:1$
- Safety Factor = 13,889

The safety factor between the NEL in the dog chronic feeding study and the TMRC_{Mod} is greater than 58,000:1 and was calculated as follows:

a. Human daily dose in 1.5 kg diet (TMRC_{Mod}) = 0.0102 mg/day

- Equivalent to = $\frac{0.0102 \text{ mg/day}}{60 \text{ kg}} = 0.00017$ mg/kg/day
- NEL: Dietary $\text{Exposure}_{\text{Mod}} = \frac{10.0 \text{ mg/kg/day}}{0.00017 \text{ mg/kg/day}} = 58{,}824:1$
- Safety Factor = 58,824

c. Worker Exposure

Worker exposure to trifluralin occurs on only a few days per year (ranging from 2.2 hours to 60.6 hours for agricultural pesticide applicators and for less than 162 hours per year for field workers).

Because exposure to workers is intermittent and the only available test data on reproductive effects (Worth et al., 1966) was obtained from a chronic feeding study, the Agency concluded that it would be inappropriate to calculate a reproductive safety factor between the 200 ppm NEL in the rat reproduction test and the level of worker exposure estimated for trifluralin.

However, teratogenic responses can theoretically result from exposure on any one day during the critical periods of gestation. Therefore, the Agency calculated teratogenic safety factors between the NEL of 450 mg/kg/day in the rabbit test and worker exposure during pesticide application and post-application.

Based upon the rabbit teratology study, these calculations are as follows:

a. NEL = 450 mg/kg/day

b. Applicator exposure, peppers (low of the range)

- 0.77 mg/yr of 2.2 hrs = 1 day of exposure[15] to 0.77 mg

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[15] Each eight-hour interval is considered to equal (1) day for these calculations.

- Equivalent to = $\frac{0.77\ \text{mg/day}}{60\ \text{kg}}$ = 0.013 mg/kg/day

- NEL:Exposure $\text{Applicator}_{\text{low}} = \frac{450\ \text{mg/kg/day}}{0.013\ \text{mg/kg/day}}$ = 34,615:1

- Safety Factor = 34,615

c. Applicator exposure, sugar cane (high of the range)

- 21.49 mg/yr of 60.6 hrs = 8 days of exposure to 21.49 mg
  = 2.69 mg/day

- Equivalent to = $\frac{2.69\ \text{mg/day}}{60\ \text{kg}}$ = 0.045 mg/kg/day

- NEL:Exposure $\text{Applicator}_{\text{high}} = \frac{450\ \text{mg/kg/day}}{0.045\ \text{mg/kg/day}}$ = 10,000:1

- Safety Factor = 10,000

d. Fieldworker exposure, cotton (low of the range)

- 32.49 ug/yr of 155 hrs = 20 days of exposure to 32.49 ug
  = 1.63 ug/day exposure
  = 0.00163 mg/day exposure

- Equivalent to = $\frac{0.00163\ \text{mg/day}}{60\ \text{kg}}$ = 0.0000272 mg/kg/day

- NEL:Exposure $\text{Fieldworker}_{\text{low}} = \frac{450\ \text{mg/kg/day}}{0.0000272\ \text{mg/kg/day}}$ = 16,544,118:1

- Safety Factor = 16,544,118

e. Fieldworker exposure, tomato (high of the range)

- 245.4 ug/yr of 162 hrs = 21 days of exposure to 245.4 ug
  = 11.69 ug/day exposure
  = 0.01169 mg/day exposure

- Equivalent to = $\frac{0.01169\ \text{mg/day}}{60\ \text{kg}}$ = 0.000195 mg/kg/day

- NEL:Exposure $\text{Fieldworker}_{\text{high}} = \frac{450\ \text{mg/kg/day}}{0.000195\ \text{mg/kg/day}}$ = 2,307,692:1

- Safety Factor = 2,307,692

I. Environmental Risk

1. Aquatic Organisms

The Agency has prepared an aquatic analysis for trifluralin (Bushong, 1978). That analysis reported that trifluralin is toxic to aquatic organisms at low levels. Trifluralin is not applied directly to water; if it were applied to water at normal field application rates, the acute toxicity level for sensitive aquatic organisms would be exceeded. When trifluralin is applied and incorporated into the soil as recommended, toxic quantities of the compound do not move into the water (see Section II,B of this document). The Agency has found that trifluralin accumulates in various fish and a species of snail, but toxic resonses to this accumulation have not been reported.

2. Terrestrial Organisms

The Agency's analysis of the risks to terrestrial organisms indicates that the acute toxicity level for trifluralin ranges from 2,000 mg/kg to greater than 10,000 mg/kg (Bushong, 1978). These levels are so high that the Agency does not consider the compound to pose a hazard to terrestrial wildlife.

III. Benefits Analysis

A. Introduction

This section describes the benefits of using Treflan on major crops and crop groups. Impacts are shown comparing the economic impact of not continuing product registrations versus a situation in which the product is registered and available for use.

The economic impact information in this section is taken from the economic analyses for Treflan prepared by the United States Department of Agriculture (USDA) and the Agency (USDA/EPA; 1978, 1978a) and from data supplied by the National Herbicide Assessment Team for Trifluralin (USDA/States, 1977). Appendix I lists the individuals who made up the latter team. These analyses are an update of the assessments prepared earlier for the petition response published in the _Federal Register_ (42 FR 40009, August 8, 1977).

Treflan is a pre-emergent herbicide used once a year to control annual grasses and some annual broadleaf weeds. Generally, Treflan is applied by low pressure spray and is incorporated into the soil within 24 hours. Its efficacy is not dependent on subsequent irrigation or rainfall.

Since its introduction into the marketplace in the early 1960's, Treflan has gained acceptance by agricultural producers of more than 50 crops, including soybeans, cotton, fruits, and vegetables. Treflan use in these crops ranges from 2.1% of the total U.S. cucumber acreage to more than 37% of U.S. soybean acreage (over 19 million acres) and almost 70% of U.S. cotton acreage (over 8 million acres).

In May 1977, a short-run analysis was completed on the economic impact of a possible Treflan suspension (USDA/EPA, 1977). That analysis concluded that agricultural income would decline by $521 million the first year after suspension. In August 1977, the Agency decided not to suspend Treflan because the benefits of its uses substantially outweighed the risks during the two-year period estimated to be necessary for completion of RPAR proceedings (42 FR 40009, August 8, 1977).

A revision of that short-run analysis completed in August 1978 indicated that the economic impact of a Treflan suspension would be a decline in agricultural income of about $573 million. This information is summarized in Table 25. The short-run analysis will not be discussed in this document since it is applicable only to a suspension action.

Instead, the Agency completed a long-run economic analysis on the impact of a possible Treflan cancellation in August 1978, as part of the pre-RPAR review of Treflan (USDA/EPA, 1978a).[16/] Because analytical precision diminishes directly with the length of time to be considered, the long-run estimates are applicable

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[16/] This report "Long-run Economic Analysis of Trifluralin" (USDA/Land Grant Universities), and data supplied by the National Herbicide Assessment Team for trifluralin (USDA/States, 1977) provides the basis for the discussion of this section.

TABLE 25

SHORT-RUN ECONOMIC IMPACT FROM A TRIFLURALIN SUSPENSION

Crop	Trifluralin Treated Acres	U.S. Acreage for this crop (%)	Output Change Without Trifluralin	Change in Weed Control Cost ($)	Value of Change in Output ($)
Cotton[1]	8,314,000	69.5	-574 M lbs.[2] -959 M lbs.[3]	+ 5,900,000	-392,400,000
Soybean	19,700,000	37.7	-95.5 M bushels	+ 36,000,000	-538,700,000
Fruits & Vegetables					
. Potatoes	72,000	5.3		+ 472,000	
. Tomatoes	337,250	68.8		+ 7,505,000	
. Peas (all)	131,610	30.0		- 505,000	- 10,852,000
. Cole Crops[4]	128,281	62.7		+ 5,385,000	
. Carrots	31,526	40.3		+ 1,185,000	
. Peppers	20,395	37.8		+ 1,169,000	
. Celery	13,510	39.4		+ 364,000	
. Cucurbits[5]	80,080	24.5		+ 2,607,000	
. Mint	7,040	7.7		+ 141,000	
. Collards/Okra	9,450	90.0		+ 1,069,000	
. Beans[6]	311,192	75.6		+ 8,324,000	
Sub Total	1,142,334	—		+ 27,716,000	- 10,852,000
Other Field Crops					
. Dry Beans	1,232,000	79.2		+ 34,108,000	- 28,468,000
. Peanuts	301,000	19.6		+ 3,303,000	- 11,840,000
. Sugar Beets	264,880	19.3		+ 11,811,000	
. Sunflowers	650,000	65.0		+ 5,827,000	- 6,142,000
Sub Total	2,477,880	—		+ 55,049,000	- 46,450,000
TOTAL	31,634,214	—		+124,665,000	-988,402,000

TABLE 25
(Continued)

Crop	Total Change in Costs and Value of Output	Income Change From Price Increase or Acreage Diversion ($)	Income Change On Acres Normally Using Trifluralin ($)	Income Change On Acres Not Normally Using Trifluralin ($)	Net Income Change ($)
Cotton[1/]	-398,300,000	+345,300,000	- 53,000,000	+149,000,000	+ 96,000,000
Soybean	-574,700,000	+376,500,000	-198,200,000	-331,200,000	-529,400,000
Fruits & Vegetables					
. Potatoes	- 472,000		- 472,000*		
. Tomatoes	- 7,505,000		- 7,505,000*		
. Peas (all)	- 10,347,000		- 10,347,000		
. Cole Crops[4/]	- 5,385,000		- 5,385,000*		
. Carrots	- 1,185,000		- 1,185,000*		
. Peppers	- 1,169,000		- 1,169,000*		
. Celery	- 364,000		- 364,000*		
. Cucurbits[5/]	- 2,607,000		- 2,607,000*		
. Mint	- 141,000		- 141,000*		
. Collards/Okra	- 1,069,000		- 1,069,000*		
. Beans[6/]	- 8,324,000		- 8,324,000*		
Sub Total	- 38,568,000		- 38,568,000		- 38,568,000
Other Field Crops					
. Dry Beans	- 62,576,000		- 62,576,000		
. Peanuts	- 15,143,000		- 15,143,000		
. Sugar Beets	- 11,811,000		- 11,811,000		
. Sunflowers	- 11,969,000		- 11,969,000		
Sub Total	-101,499,000		-101,499,000		-101,499,000
TOTAL[7/]	-1,113,067,000	+721,800,000	-391,267,000	-182,200,000	-573,467,000

1/ Midpoint estimate of data from price elasticities of demand of -0.3 and -1.0.
2/ Lint cotton
3/ Cottonseed
4/ Cabbage, broccoli, brussel sprouts, cauliflower only.
5/ Watermelons, cantaloupes, honeydews, cucumbers only.
6/ Snapbeans, lima beans, southern peas only.
7/ These totals may not sum exactly due to rounding errors.
*/ This impact is based only upon increased production costs. Yield/quality reductions were not expected for this crop.

only to a period of from three to five years after the time of a possible cancellation.[17]

B. Long-Run Economic Impact Analysis

If Treflan were cancelled, it is estimated that annual agricultural income would decline by $313 million[18/]; Treflan users would lose $564.2 million and non-users would gain $250.9 million (Table 26). The $564.2 million loss to users includes a loss of $596.1 million due to a decrease in yield, plus an additional $262.9 million in increased weed control costs. This gives a total reduction in revenues of $859 million, which is partially offset by a gain of $294.8 million from shifting to other crops and higher crop prices.

Cancelling Treflan would also cost consumers of agricultural products at least $328.5 million per year. However, this long-run economic analysis used partial budgeting techniques, and this total annual figure is the only consumer impact which was estimated. The rest of the analysis deals with changes in agricultural income.

I. Cotton

Based on the average number of acres planted in cotton from 1971 to 1976, Treflan is used on approximately 8.3 million acres of cotton per year (70% of the total U.S.

17/ Impacts are generally expressed in terms of 1974-76 dollars. Both farm input and outut prices representative for 1979 would be generally higher due to inflation and the atypically large increases in foreign demand.

18/ The numbers used in this section are taken from the text of USDA/EPA (1978a) which are rounded off. The supporting figures which were based on estimates for the crop years 1973-1976 can be found in the tables of that document.

TABLE 26

LONG-RUN ECONOMIC IMPACT FROM A TRIFLURALIN CANCELLATION

Crop	Trifluralin Treated Acres	U.S. Acreage for this crop (%)	Output Change Without Trifluralin	Change in Weed Control Cost ($)	Value of Change in Output ($)
Cotton	8,314,000	69.5	-286 M lbs.[1] -479 M lbs.[2]	+ 32,700,000	-195,600,000
Soybean	19,700,000	37.7	-61.5 M bushels	+150,300,000	-346,800,000
Fruits & Vegetables					
. Potatoes	72,000	5.3		+ 387,000	
. Tomatoes	337,250	68.8		+ 7,505,000	
. Peas (all)	131,610	30.0		- 462,000	- 10,398,000
. Cole Crops[3]	128,281	62.7		+ 5,385,000	
. Carrots	31,526	40.3		+ 1,185,000	
. Peppers	20,395	37.8		+ 1,169,000	
. Celery	13,510	39.4		+ 364,000	
. Cucurbits[4]	80,080	24.5		+ 2,607,000	
. Mint	7,040	7.7		+ 141,000	
. Collards/Okra	9,450	90.0		+ 897,000	
. Beans[5]	311,192	75.6		+ 6,729,000	
Sub Total	1,142,334	—		+ 25,907,000	- 10,398,000
Other Field Crops					
. Dry Beans	1,232,000	79.2		+ 32,737,000	- 26,935,000
. Peanuts	301,000	19.6		+ 4,031,000	- 10,692,000
. Sugar Beets	264,880	19.3		+ 11,811,000	
. Sunflowers	650,000	65.0		+ 5,369,000	- 5,670,000
Sub Total	2,477,880	—		+ 53,948,000	- 43,297,000
TOTAL	31,634,214	—		+262,855,000	-596,095,000

TABLE 26
(Continued)

Crop	Total Change in Cost and Value of Output ($)	Income Change From Price Increase or Acreage Diversion ($)	Income Change On Acres Normally Using Trifluralin ($)	Income Change On Acres Not Normally Using Trifluralin ($)	Net Income Change ($)
Cotton	-228,300,000	+ 76,500,000	-151,800,000	+ 36,000,000	-115,800,000
Soybean	-497,100,000	+218,300,000	-278,800,000	+214,900,000	— 63,900,000
Fruits & Vegetables					
. Potatoes			- 387,000*		
. Tomatoes			- 7,505,000*		
. Peas (all)			- 9,936,000		
. Cole Crops[3]			- 5,385,000*		
. Carrots			- 1,185,000*		
. Peppers			- 1,169,000*		
. Celery			- 364,000*		
. Cucurbits[4]			- 2,607,000*		
. Mint			- 141,000*		
. Collards/Okra			- 897,000*		
. Beans[5]			- 6,729,000*		
Sub Total	- 36,305,000		- 36,305,000		- 36,305,000
Other Field Crops					
. Dry Beans			- 59,672,000		
. Peanuts			- 14,723,000		
. Sugar Beets			- 11,811,000		
. Sunflowers			- 11,039,000		
Sub Total	- 97,245,000		- 97,245,000		- 97,245,000
TOTAL	858,950,000	+294,800,000	-564,150,000	+250,900,000	-313,250,000

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[1] Lint cotton

[2] Cottonseed

[3] Cabbage, broccoli, brussel sprouts, cauliflower only.

[4] Watermelons, cantaloupes, honeydews, cucumbers only.

[5] Snapbeans, lima beans, southern peas only.

* This impact is based only upon increased production costs. Yield/quality reductions were not expected for this crop.

planted cotton acreage). If Treflan were cancelled, users could expect their yields to decrease and weed control costs to increase. The total value of this loss in yields is estimated to be $195.6 million (based on an average yield from 1971 to 1976, and a price for lint cotton of $0.60 per pound and cottonseed of $0.05 per pound).[19] Assuming that alternative herbicide prices would be unchanged, that alternative herbicides would be available in sufficient quantities, and that there would be sufficient hand labor and mechanical equipment available at current market prices, the cost of controlling weeds would increase by $32.7 million.[20] It is expected that the price of cotton would increase, partially offsetting the loss to Treflan users by $76.5 million.[21] In making this determination, the Agency assumed that some cotton previously going to the export market would flow to the domestic market in response to the cotton shortage caused by reduced yields. The net loss of income to cotton producers using Treflan would be $151.8 million. This includes a $195.6 million loss due to reduced cotton yield, a $32.7 million increase in weed control costs, and a $76.5 million offsetting revenue gain from a cotton price increase. Because the price for cotton would increase, the income of farmers who do not use Treflan would increase by $36 million. The total income change for all cotton growers would be a decrease of $115.8 million (-$151.8 million for Treflan users; + $36.0 million for non-users).

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[19] Gaede, 1979. This is a projection based on 1973-1977 data.
[20] The herbicides selected as possible alternatives to Treflan will vary according to region. Costs are estimated on one application of either fluchloralin, dinitramine, pendimethalin, profluralin, fluometuron, diuron, prometryn, norflurazon, DCPA, bensulide, alachlor, other dinitroanilines, various mixtures, or cultivation and hoeing.
[21] A price elasticity of demand at - 1.5 was used for lint cotton which increased price by 2.2 cents per pound. No change in cottonseed price was assumed.

2. Soybeans

Based on the average number of acres planted in soybeans from 1974 to 1976, Treflan is used on approximately 19.7 million acres of soybeans per year (38% of the total acres planted in soybeans in the U.S.). As with cotton, if Treflan were cancelled, users could expect yields to decrease and weed control costs to increase. The value of the yield reduction is estimated to be $346.8 million (based on a soybean price of $5.64 per bushel).22/ Assuming that alternative herbicide prices would be unchanged, that alternative herbicides would be available in sufficient quantities, and that there would be sufficient hand labor and mechanical equipment at current market prices, the cost of controlling weeds would increase by $150.3 million.23/ It is expected that the price of soybeans would increase, yielding an additional $209.1 million for Treflan users plus $9.2 million in revenue from acres shifted to corn.24/

22/ The soybean base price is a weighted average from 1974-1976.

23/ The herbicides selected as possible alternatives to Treflan will vary according to region. The analyzed alternatives are metribuzin, other dinitroanilines, alachlor alone, alachlor and metribuzin or linuron or naptalam, vernolate, chloramben, linuron and additional cultivations, and non-chemical controls: cultivation, rotation to corn, and delayed planting.

24/ Price changes as a result of decreased soybean output were estimated using revenue flexibilities from a simultaneous equation model and are an increase of $0.60 per bushel for soybeans and a decrease of $0.069 per bushel for corn for each 100 million bushel changes in production. The base price for soybeans is $5.64 per bushel and for corn, $2.68 per bushel (1974-1976 average). It is estimated that 340,000 soybean acres would be shifted to corn.

This would mean a total offsetting increase in revenues of $218.3 million. Thus, the net income loss for soybean producers using Treflan would be $278.8 million (- $346.8 million in the value of soybean yield; - $150.3 million in increased weed control costs; + $209.1 million offsetting revenue gain from increased soybean value; + $9.2 million from acres shifted to corn). The income for non-users of Treflan would increase by $214.9 million (from a $337.2 million increase in the value of their soybeans as a result of a price increase, and a $122.3 million loss from a decrease in corn prices). The total income change for soybean and corn growers would be a decrease of $63.9 million (- $278.8 million for Treflan users; + $214.9 million for non-users).

3. Fruits and Vegetables

Based on the average number of planted acres from 1974 to 1976, Treflan is used on approximately 1.1 million acres of fruits and vegetables. If Treflan were cancelled, weed control costs would increase, but yields would decrease only for peas. The value of this yield reduction is estimated to be $10.4 million.[25] Assuming that alternative herbicide prices would be unchanged, that alternative herbicides would be available in sufficient quantities, and that there would be sufficient hand labor and mechanical equipment available at current market prices, the cost of controlling weeds would increase by $25.9 million ($16.0 million for hand weeding, $5.9 million for alternative herbicides, $4.0 million for mechanical cultivation).[26] Price changes were not estimated for fruits and vegetables due to a possible Treflan cancellation. The income loss for vegetable and fruit growers using Treflan is estimated to be $36.3 million (due to a $10.4 million reduction as a result of reduced pea yields, and $25.9 million in increased weed control costs).

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[25] Assumes an average pea yield of 1.3 tons/acre in the U.S. and a three year average price of $204/ton. Average yields were estimated to decline by 5% on profluralin-treated acres, 20% on dalapon-treated acres, and 40% on acres using cultivation only.

4. Other Field Crops

Based on the average number of planted acres from 1974 to 1976, Treflan is used on approximately 2.5 million acres of dry beans, peanuts, sugar beets, and sunflowers. If Treflan were cancelled, current users could expect their yields to decrease (except for sugar beets) and weed control costs to increase. The value of yield reductions is estimated to be $43.3 million (based on average yields and prices for 1974-1976).[27] Assuming that alternative herbicide prices would be unchanged, that alternative herbicides would be available in sufficient quantities, and that there would be sufficient hand labor and mechanical equipment available at current market prices, the cost of controlling weeds would increase by $53.9 million (an increase of $48.5 million for hand weeding, $7.4 million for mechanical cultivation, and a decrease of $1.9 million in the cost of alternative herbicides).[28] No estimates were made for price changes due to a possible Treflan cancellation. The income loss to growers of dry beans, peanuts, sugarbeets, and sunflowers is estimated to be $97.2 million (- $43.3 million reduction in the value of yield; - $53.9 million in increased weed control costs).

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[26] Alternative herbicides considered were diphenamid, bensulide, napropamide, pebulate, dalapon, EPTC, profluralin, nitrofen, dinitramine, oil, chlorpropham, linuron, DNBP, alachlor, metribuzin, terbacil, chloramben, naptalam, various chemical combinations, mechanical cultivation and hand weeding were also considered where applicable.

[27] It is estimated that yield losses will be 5-10% for sunflower, 5-15% for peanuts, 0-7% for dry beans (except in Idaho where an additional 0 to 20% yield loss could result due to shattering), and no yield change for sugarbeets.

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[28] It is estimated that there would be a decreased alternative herbicide cost for dry beans of $6.9 million and an increase cost for peanuts ($1.0 million), sunflowers ($3.6 million), and sugarbeets ($0.4 million. Alternatives that were considered are: profluralin, dinitramine, EPTC, alachlor,, chloramben, DNBP, and hand weeding for dry beans; alachlor vernolate, dinitramine, mechanical and hand weeding for peanuts; EPTC, mechanical mechanical cultivation and hand weeding for sugarbeets; chloramben, profluralin, EPTC, and mechanical cultivation for sunflowers.

IV. Risk-Benefit Analysis of Alternative Courses of Action

A. Introduction

The Agency has determined that both technical and formulated trifluralin is contaminated with low levels of the N-nitroso contaminant NDPA, a demonstrated oncogen in rats, mice, and hamsters, and a mutagen in bacteria, yeast, and in an *in vitro* mammalian cell culture. Treflan (the trade name for trifluralin) is, therefore, presumed to be an oncogen and a mutagen.[29]

B. Options

The Agency has considered three regulatory options:

(1) to cancel registrations of all products containing trifluralin,

(2) to allow continued trifluralin use without further regulation, or

(3) to allow continued trifluralin use only if its NDPA contamination does not exceed a certain level.

(1) Cancell Registrations of all Products Containing Trifluralin

Table 27 summarizes information from the risks and benefits analysis for the agricultural uses of the predominant

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[29] Under 40 CFR § 162.11(a)(3)(ii), "A rebuttable presumption shall arise if a pesticide's ingredient(s)... meet or exceed any of the following criteria for risk,... Induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure; or induces mutagenic effects, as determined by multitest evidence." NDPA-contaminated Treflan would also be considered a mutagen under the Proposed Mutagenicity Guidelines. 43 FR 37336, August 22, 1978.

TABLE 27

RISK/BENEFIT COMPARISON OF TRIFLURALIN USES[1]

Use	Number of Workers	AG - Worker Cancer Cases[2]	Dietary Cancer Cases[3]	Long-Run Economic Analysis[5] Farm Income Losses From a Trifluralin Cancellation
Soybeans	193,000	0.03	0.17	63,900,000
Cotton	64,000	<0.01	0.52	115,800,000
Potatoes	1,800	<0.01	0.14	387,000
Tomatoes	13,500	<0.01	0.98	7,505,000
Cole Crops[4]	4,200	<0.01	0.30	5,385,000
Carrots	700	<0.01	1.91	1,185,000
Peppers	2,300	<0.01	0.02	1,169,000
Celery	200	<0.01	0.06	364,000
Cucurbits[6]	6,000	<0.01	0.35	2,607,000
Mints[7]	50	<0.01	0.10	141,000
Greens[8]	3,500	<0.01	0.09	897,000[9]
Beans[10]	23,700	<0.01	1.36	66,401,000[11]
Peas[12]	3,100	<0.01	0.05	9,936,000
Peanuts	4,500	<0.01	0.03	14,723,000
Sugar Beets	5,200	<0.01	0.21[13]	11,811,000
Sunflower	5,500	<0.01	0.01	11,039,000
Sugar Cane	100	<0.01	[13]	PNA[14]
Tree/Vine[15]	4,000	<0.01	0.79	PNA
Hops	50	<0.01	<0.01	PNA
Dill	< 50	<0.01	0.01	PNA
Mustard Seed	50	<0.01	0.01	PNA
Safflower	1,000	<0.01	0.01	PNA
Spring Wheat	1,000	<0.01	0.06	PNA
Alfalfa	300	<0.01	[16]	PNA
Corn Grain			0.49	PNA
Asparagus			0.07	PNA
Subtotal	337,800	<0.01	7.76	313,250,000
Commercial Applicators	3,800	<0.01	NA	NA
Total	340,000	<0.04	<8.00	313,250,000

TABLE 27
(Continued)

1/ This estimate is based upon a maximum theoretical calculation which assumes that crop residues of NDPA exist following Treflan treatment. Such residues have not been detected in a number of species analyzed at a level of sensitivity of 0.1 to 0.2 ppb. This estimate assumes an NDPA level of 5 ppm in Treflan. To calculate the approximate risk at 1 ppm NDPA in Treflan divide these numbers by 5.
2/ Applicators, incorporators, mixers, loaders.
3/ For U.S. population of 2.2 x 10^8 from 70-year exposure period.
4/ Cole crops: cauliflower, broccoli, brussel sprouts, cabbage.
5/ Numbers are negative unless otherwise indicated. They reflect annual economic impact estimates for the immediate 3-5 years following possible cancellation.
6/ Curcurbits: cantaloupes, watermelon, cucumbers.
7/ Mints: spearmint, peppermint.
8/ Greens: kale, collards, turnips, mustard.
9/ Collards only.
10/ Beans: guar, mung, lima, snap, southern peas, dry beans.
11/ Snap beans, lima, southern peas and dry beans only.
12/ Peas: dry, English, field.
13/ Dietary parameters combine sugar cane and sugar beets.
14/ PNA: parameter not assessed.
15/ Tree/Vine: grapes, citrus, nut trees, stone fruits.
16/ No human food use.

form of trifluralin, Treflan EC. The risk estimates are made for Treflan contaminated with 5 ppm NDPA.*/ The risk shown is that for cancer to applicators through work-related exposure and to the general public through dietary exposure. Other uses, including nursery, landscape, and home uses, involve application of the compound on smaller areas (each applicator would use smaller amounts of trifluralin and would have less exposure time than his agricultural counterpart) or involve products with much less trifluralin and therefore less NDPA in their composition. Use of such products would confer only a fraction of the risk shown for agricultural uses. In addition, because of the low trifluralin and NDPA levels in many of these other products, it is not possible to measure NDPA exposure from their use.

There are more than 300,000 workers involved with Treflan application operations to agricultural sites (including mixing, loading, application, and incorporation). The number of workers applying the herbicide to a particular crop ranges from less than 50 for dill to almost 200,000 for soybeans. Exposure to NDPA from Treflan use ranges from a low of 0.18 ug per year in greens to a high of 5.05 ug per year in sugarcane. Workers applying the product have an estimated risk of developing cancer from such exposure on the order of one in 10,000,000. The Agency estimates this would result in less than one case of cancer in the entire applicator population.

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*/ This level would be divided by 5 to derive an estimate of approximate risk from Treflan contaminated at 1 ppm NDPA.

The Agency estimated risk to field workers entering Treflan-treated fields to be about 1 in 10,000,000 using a worst-case model and to be negligible in another model. Risk from contact with contaminated soil would be of the same magnitude or less.

The Agency has estimated the dietary exposure to NDPA from Treflan use to be about 8.0×10^{-8} mg/kg diet/day from all crops treated with this herbicide. This would result in an approximate risk of less than 9×10^{-9} for the U.S. population over a 70-year lifetime of ingesting Treflan-treated crops which might contain NDPA. It must be emphasized that this estimate is very imprecise and conservative since analyses of Treflan-treated crops at harvest have not succeeded in detecting NDPA residues, and since measurable levels of such residues are not likely because of the low product contamination.

Technical and formulated trifluralin preparations have not shown mutagenic activity in numerous test systems, however, the principle contaminant of both (NDPA) has induced point mutations in bacterial and mammalian *in vitro* tests and altered genetic processes in a yeast. Limited studies appear to show that high concentration of trifluralin have the capacity to disrupt formation or function of the spindle apparatus in dividing cells, thereby having the potential to cause abnormal segregation of chromosomes (non-disjunction).

Existing data are not adequate to determine or to quantify any risk for gene or DNA interactions posed by NDPA contaminated trifluralin. However, since existing data from studies with NDPA contaminated trifluralin preparations seem to contradict positive results obtained in mutagenicity assays with NDPA alone, and because human exposure to NDPA from trifluralin use is extrmely low, the Agency considers the potential for such a hazard to be low. In addition, data on transport of NDPA to germinal tissue and its metabolism to active forms therein is inconclusive.

With respect to spindle effects, the Agency is not certain whether trifluralin itself, a metabolite or a contaminant in this herbicide is the active component in this regard. The existing data are not adequate to demonstrate the existence of a significant risk from effects to the cell division spindle at estimated trifluralin or NDPA exposure levels.

The Agency assessed the long-run impact of cancelling Treflan. The net loss of farm income was estimated to be greater than $300 million per year for 3- to 5- year period following a cancellation. This figure does not include some of the minor use crops treated with this herbicide.

If all Treflan registrations were cancelled, therefore, the carcinogenic and mutagenic risks which derive from

Treflan use would be eliminated and farm income would decrease by approximately $300 million per year for the years immediately following cancellation.

(2) Allow Continued Trifluralin Use Without Further Regulation

This option would not reduce the carcinogenic and mutagenic risks associated with Treflan use, as described in the previous section. Furthermore, NDPA contamination of Treflan could increase above the current level, causing an increase in risk without any increase in benefits. Farm income, however, would not suffer any of the $300 million per year estimated loss due to cancellation.

(3) Allow Continued Trifluralin Use Only if its NDPA Contamination Does Not Exceed a Certain Level

The single U.S. producer of Technical trifluralin has informed the Agency that it now produces the technical and end use product contaminated with 1 ppm NDPA or less. If the Agency were to require that this level of purity be maintained, risk would be reduced from that associated with 5 ppm NDPA contamination. There would be no impact on benefits; farm income would be unchanged because all Treflan uses would continue, and the single trifluralin producer would not experience any added expense[30] since it has already made the necessary modifications to produce trifluralin at 1 ppm NDPA or less.

V. Proposed Regulatory Action

The Agency proposes to adopt option 3 -- to allow continued trifluralin use only if its NDPA contamination does not exceed a certain level. At the current low level of NDPA contamination (1 ppm or less), and because of low exposure and substantial benefits, the Agency has determined that the benefits of Treflan use outweigh the risks. Therefore, the Agency has decided not to unconditionally cancel all trifluralin registrations (Option 1). The Agency has determined, however, that use of trifluralin contaminated with greater than 1 ppm of NDPA would be unreasonable, because the risks would be increased unnecessarily with no offsetting increase in benefits (Option 2). The only active producer has demonstrated, furthermore, that it is technically feasible to produce trifluralin at this level of contamination. Therefore, the Agency proposes to issue a section 6(b)(1) notice of intent to cancel all trifluralin registrations[31] unless registrants amend their terms and conditions of registration to limit the NDPA content in trifluralin to a level not to exceed 1 ppm.[32] In regard to those who are currently operating under State-approved trifluralin registrations with Federal trifluralin registration applications pending final EPA decision[33] and those who may have submitted applications for new trifluralin registrations, their applications will be denied unless those applications are amended to satisfy the requirement that the NDPA content in trifluralin does not exceed 1 ppm. Once these applications are amended to comply with these requirements, they will continue to be reviewed by the Agency to assess whether all registration requirements have been satisfied.

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[30] This analysis pertains to the single Treflan registrant which currently produces Treflan as well as other registrants with the current capability of producing Treflan at 1 ppm NDPA or less. With regard to potential registrant-producers who would be unable to meet the NDPA contamination level requirement without substantially increased cost, a separate risk/benefit analysis would be required which would examine the risks and benefits of Treflan at the higher NDPA contamination. That analysis would also examine the cost of reducing the NDPA contamination to 1 ppm and the reduction of risk achieved by that limitation.

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[31] Some registrants have received state registrations for trifluralin to meet special local needs under the authority of 24(c) of FIFRA. These registrations are federal registrations governed by FIFRA. They are subject to this proposed 6(b)(1) notice of intent to conditionally cancel all trifluralin registrations.

[32] Once registrants have amended their terms and conditions of registration to comply with the maximum NDPA contamination requirement, it will be unlawful (under sections 12(a)(1)(c) and (E) of FIFRA) to sell or distribute trifluralin products whose registrations have been so amended if they are contaminated with NDPA at levels greater than 1 ppm.

[33] Under 40 CFR 162.17, all State-registered pesticide products, unless governed by sectioon 24(c) of FIFRA, must be registered under FIFRA. Pending a final EPA registration decision, however, State registrants may continue to sell or distribute the pesticide product if solely within intrastate commerce.

The label amendment proposed by this notice shall appear on the label under the inert ingredients section of the ingredients statement and shall read as follows:

N-nitroso-di-n-propylamine (NDPA).....< 1 ppm.

The amendment to the confidential statement of formula proposed by this notice shall appear in that statement under the inert ingredients section of the ingredients statement and shall read as follows:

N-nitroso-di-n-propylamine (NDPA)......< 1ppm.

The trifluralin registrants will be required to certify that this level is an upper limit in accordance with §163.61-6 of the Guidelines for Registration of Pesticides in the United States, Subpart D, Chemistry Requirements, as proposed on July 10, 1978 [43 FR 29709-29710]. A registrant who distributes a pesticide product, the chemical composition of which differs from the amended chemical composition statement, will be in violation of FIFRA section 12(a)(1)(C) and subject to sanctions under section 13 and 14 of FIFRA.

The registrants of trifluralin must also advise the Agency as to quality control procedures they will institute to assure the Agency that the level of NDPA as stated on the label is not exceeded. In addition, registrants must maintain accurate quality control records on these products and make such records available to the Agency on demand.

Finally, the Agency considers the data on the mutagenic potential (including DNA, gene and chromosomal effects) of this compound (including it benzimidazole metabolites) to be inadequate for a precise determination of risk. Additionally, the Agency considers the data on reproduction and teratology to be inadequate. FIFRA Section 3(c)(2)(B) states in part, that:

> (i) If the Administrator determines that additional data are required to maintain in effect an existing registration of a pesticide, the Administrator shall notify all existing registrants of the pesticide to which the determination relates and provide a list of such registrants to any interested person.

The Agency, therefore, will require registrants of products containing trifluralin to test trifluralin and provide the Agency with data concerning the mutagenic potential of this compound and its benzimidazole metabolites see Section III (mutagenicity risk assessment). Additionally the Agency will require the registrants to perform new reproduction tests (see Section III. H. 1 of this PD) and teratology tests (see Section III. H. 2 of this PD) to satisfy data gaps existing for those criteria. The Agency will specify requirement for filling these data gaps consistent with the expeditious resolution of these issues.

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John J. Neylan - PTSED, OE

Appendix I

NATIONAL HERBICIDE ASSESSMENT TEAM
for Trifluralin (Treflan)
St. Louis, Missouri
March 9, 10, 11, 1977

Member	Affliation
Bob Anderson	ARS - Minnesota
Gale Buchanan	Auburn University
Herman Delvo	ERS - Washington, DC
Clyde Dowler	ARS - Georgia
Stanford Fertig	ARS - Washington, DC
Stan Heatham	University of Arizona
John Holstun	ARS - Missouri
John Miller	ARS - California
Art Lange	University of California
Phil Kearney	ARS - Beltsville
Chester McWhorter (Co Chairman)	ARS - Mississippi
Arnie Paulsen	Iowa State University
Roman Romanowski	Purdue University
Fred Slife (Chairman)	University of Illinois
Loyd Wax	ARS - Illinois
Allen Wiese	Texas A&M

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Bob Anderson - ARS, USDA, Minnesota
Dr. Gayle Buchanan - Auburn University
Dr. Herman Delvo - ERS, USDA, Washington, D.C.
Clyde Dowler - ARS, USDA, Georgia
Dr. Stanford Fertig, ARS, Washington, D.C.
Dr. Stan Heatham - University of Arizona
John Holstun - ARS, USDA, California
Dr. Phil Kearney - ARS, Washington, D.C.
Dr. Art Lange - University of California
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John Miller - ARS, USDA, California
Dr. Arnie Paulsen, Iowa State University
Dr. Roman Romanowski - Purdue University
Dr. Fred Slife - (Chairman), University of Illinois
Loyd Wax - ARS, USDA, Illinois
Dr. Allen Wiese - Texas A&M

Other Contributors

Homer Hall - Chief Branch 1, SPRD, OPP

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01/10/79            FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  000158        WASATCH CHEMICAL DIVISION ENTRADA IND INC
                   P O BOX 6219
                   SALT LAKE CITY UT 84105

     **************** PRODUCT NAME ****************

   **00420*  MORGRO SYSTEMIC ROSE FOOD TRIPLE ACTION

   **00452*  MORGRO GRASS & WEED SEED KILLER WITH TREFLAN

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  000192        DEXOL INDUSTRIES
                   1450 W 228TH ST
                   TORRANCE, CA 90501

     **************** PRODUCT NAME ****************

   **00086*  DEXOL DE-SEED

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  000239        CHEVRON CHEMICAL COMPANY
                   ORTHO DIVISION                             4152359300
                   940 HENSLEY WAY
                   RICHMOND CA 94804

     **************** PRODUCT NAME ****************

   **02262*  ORTHO ROSE & FLOWER WEED AND FEED GRANULES 8-24-8

   **02263*  ORTHO WEED & FEED GRANULES 12-16-8

   **02292*  ORTHO 3-WAY ROSE & FLOWER CARE 8-12-4 PLANT FOOD WITH "SYSTEMIC IN
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                    **** PRODUCT SEARCH LISTING ****                    PAGE

01/10/79            FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN


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  *REGISTRANT*        *NAME AND ADDRESS*

  *  000538        SCOTT O M & SONS COMPANY
                   GOVERNMENT-INDUSTRIAL RELATIONS            5136440011
                   MARYSVILLE OH 43040

     **************** PRODUCT NAME ****************

   **00083*  SCOTTS SHRUB & TREE WEED PREVENTER PLUS FERTILIZER 20-4-8

   **00102*  STOP WEEDS BEFORE THEY START


************************************************************************************

  *REGISTRANT*        *NAME AND ADDRESS*

  *  000539        SEARS ROEBUCK & COMPANY
                   SEARS TOWER/DEPT 671/15TH FLOOR            3128755423
                   SEARS TOWER DEPT. 766/58TH FLOOR
                   CHICAGO IL 60684

     **************** PRODUCT NAME ****************

   **00282*  SEARS LOGO TRIPLE ACTION ROSE FOOD 11-6-8


************************************************************************************

  *REGISTRANT*        *NAME AND ADDRESS*

  *  000572        ROCKLAND CHEMICAL CO. INC.
                                                              2015751322
                   P.O. BOX 809
                   CALDWELL, NJ 07006

     **************** PRODUCT NAME ****************

   **00200*  ROCKLAND GARDEN CLEAN WITH TRIFLURALIN

   **00226*  ROCKLAND GARDEN CLEAN PLUS

   **00260*  STOP & GRO WEEDS AS IT FEEDS 7-8-7
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                   **** PRODUCT SEARCH LISTING ****                PAGE      3

01/10/79           FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*        *NAME AND ADDRESS*

   * 000602         RALSTON PURINA COMPANY
                                                        314 9822356
                    CHECKERBOARD SQUARE
                    ST LOUIS MO 63188

      ***************** PRODUCT NAME *****************

    **00155*  PURINA WEED-KILL GRANULES

*******************************************************************************

   *REGISTRANT*        *NAME AND ADDRESS*

   * 000635         GROWER SERVICE CORP
                    DIV. OF GROWER SERVICE CORP.
                    BOX 18037
                    LANSING MI 48901

      ***************** PRODUCT NAME *****************

    **00665*  E Z FLO TRIFLURALIN EC

*******************************************************************************

   *REGISTRANT*        *NAME AND ADDRESS*

   * 000769         WOOLFOLK CHEMICAL WORKS, INC.
                    P.O. BOX 938
                    FT. VALLEY, GEORGIA 31030

      ***************** PRODUCT NAME *****************

    **00377*  SECURITY E Z E GARDEN WEED KILLER

    **00378*  SECURITY CRABGRASS KILLER FOR LAWNS
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                     **** PRODUCT SEARCH LISTING ****                    PAGE

 01/10/79            FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*         *NAME AND ADDRESS*

   *  000961        LEBANON CHEMICAL CORPORATION
                    P.O. BOX 180
                    LEBANON, PENNSYLVANIA 17042

      **************** PRODUCT NAME ****************

    **00250*  LEBANON FLOWER AND SHRUBBERY BED WEED CONTROL CONTAINS TREFLAN

    **00280*  PREEN THE WEED PREVENTER

    **00283*  EVER PREEN WEEDS AS IT FEEDS EVERGREENS AND AZALEAS

    **00287*  ROSE & FLORA PREEN 7-8-5 SPECIAL ORGANIC FORMULA

    **00289*  GREENVIEW CRABGRASS & DANDELION KILLER

    **00293*  CRABGRASS KILLER AND PREVENTER

*****************************************************************************************

   *REGISTRANT*         *NAME AND ADDRESS*

   *  001471        ELANCO PRODUCTS DIVISION ELI LILLY
                    ATTN: RALPH HILL                            3172612535
                    PO BOX 1750
                    INDIANAPOLIS IN 46206

      **************** PRODUCT NAME ****************

    **00035*  TREFLAN E. C.

    **00041*  TREFMID 50W

    **00059*  TREFLAN GRANULAR

    **00065*  TREFLAN EMULSIFIABLE CONCENTRATEFOR PROFESSIONAL USE IN ORNAMENTA

    **00066*  TREFLAN 5G FOR PROFESSIONAL USE IN ORNAMENTALS

    **00068*  TREFMID W.P.

    **00070*  ELANCO TRIFLURALIN TECHNICAL 95%
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**CONTINUE REGISTRANT 001471

   **00072*  ELANCO TRIFLURALIN EMULSIFIABLE CONCENTRATE 44.5*


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  *REGISTRANT*        *NAME AND ADDRESS*

  *  001598        FOX INC
                   PO BOX 2419
                   RALEIGH, NC 27602

     **************** PRODUCT NAME ****************

   **00215*  GREEN SHRUB WEEDER


********************************************************************************

  *REGISTRANT*        *NAME AND ADDRESS*

  *  002217        PBI-GORDON CORPORATION
                                                          9133428781
                   300 SO 3RD ST
                   KANSAS CITY KS 66118

     **************** PRODUCT NAME ****************

   **00480*  GORDON'S WEEDER GRANULES


********************************************************************************

  *REGISTRANT*        *NAME AND ADDRESS*

  *  002491        KOOS INC
                   4500 13TH CT
                   KENOSHA WI 53140

     **************** PRODUCT NAME ****************

   **00291*  HOLIDAY FLOWER BED WEED CONTROL
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                        **** PRODUCT SEARCH LISTING ****                   PAGE

 01/10/79              FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  002749          ACETO CHEMICAL COMPANY INC
                      AGRICULTURE DIV.                             2128982300
                      126-02 NORTHERN BLVD
                      FLUSHING NY 11368

     **************** PRODUCT NAME ****************

   **00219*  TRIFLURALIN 4 EC

   **00294*  TRIFLURALIN TECHNICAL HERBICIDE

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  003442          USS AGRI-CHEMICALS DIV US STEEL CORP
                      PO BOX 1685
                      ATLANTA GA 30301

     **************** PRODUCT NAME ****************

   **00573*  USS VERTAGREEN TRIPLE DUTY ROSE & FLOWER TREATMENT

********************************************************************************
   *REGISTRANT*        *NAME AND ADDRESS*

   *  003770          ECONOMY PROD COMPANY

                      1125 NORTH 11TH ST.                          4023411070
                      OMAHA, NE 63102

     **************** PRODUCT NAME ****************

   **00169*  ECONOMY FLOR-ADORN

   **00170*  CLEAN GRASS & WEED CONTROL TREFLAN FOR SHRUBBERY & FLOWER BEDS

   **00194*  ROSE ADORN WEED AND FEED ROSES
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                    **** PRODUCT SEARCH LISTING ****                    PAGE      7

  1/10/79           FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  004822         S.C. JOHNSON AND SONS INC
                     LAW DEPT                                  4145542000
                     1525 HOWE STREET
                     RACINE, WI 53403

      **************** PRODUCT NAME ****************

    **00123*  JOHNSON YARD MASTER GARDEN WEED PREVENTER

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  005481         AMVAC CHEMICAL CORP
                     4100 EAST WASHINGTON BLVD
                     LOS ANGELES, CA 90023

      **************** PRODUCT NAME ****************

    **00172*  TRIFLURALIN EMULSIFIABLE CONCENTRATE

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  005632         CORENCO CORPORATION
                     525 WOBURN STREET
                     TEWKSBURY MA 01876

      **************** PRODUCT NAME ****************

    **00016*  TIMBERLINE WITH TREFLAN
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           **** PRODUCT SEARCH LISTING ****                    PAGE      8

1/10/79           FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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  *REGISTRANT*       *NAME AND ADDRESS*

  *  005887        BLACK LEAF PROD COMPANY
                   667 N STATE ST
                   ELGIN IL 60120

     **************** PRODUCT NAME ****************

   **00062*  BLACK LEAF SYSTEMIC "3"


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  *REGISTRANT*       *NAME AND ADDRESS*

  *  006720        SOUTHERN MILL CREEK PRODUCTS COMPANY INC
                   BOX 1096
                   TAMPA FL 33601

     **************** PRODUCT NAME ****************

   **00066*  GARDEN WEEDER CONTAINS TREFLAN USE BEFORE WEEDS APPEAR


*********************************************************************************

  *REGISTRANT*       *NAME AND ADDRESS*

  *  006735        TIDE PRODUCTS INC.
                   ATTN: M.W. MARSH                          5123834901
                   BOX 1020
                   EDINBURG, TEXAS 78539

     **************** PRODUCT NAME ****************

   **00215*  TIDE TRIFLURALIN EC

   **00229*  TIDE WEED AND FEED WITH TREFLAN

   **00233*  TIDE WEED & FEED WITH TREFLAN FOR COTTON & SOYBEANS

   **00234*  TIDE WEED & FEED WITH TREFLAN FOR COTTON & SOYBEANS

   **00236*  TIDE WEED AND FEED WITH TREFLAN
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7/10/79            FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  006993         GERMAINS INC
                    4820 E 50TH ST
                    LOS ANGELES CA 90058

     ***************** PRODUCT NAME *****************

    **00029*  GERMAIN'S ROSE GUARD 8-12-6

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  007001         OCCIDENTAL CHEMICAL CO
                    P O BOX 198
                    LATHROP, CA 95330

     ***************** PRODUCT NAME *****************

    **00193*  TRIFLURALIN 4EC

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  009499         NATIONAL CHELATING COMPANY
                    6549 E COMPTON BLVD
                    PARAMOUNT, CA 90723

     ***************** PRODUCT NAME *****************

    **00004*  PRE-SEEDER WEEDER GRANULAR
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11/10/79            FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN


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   *REGISTRANT*        *NAME AND ADDRESS*

   *  011214         TARGET CHEMICAL COMPANY
                     17710 STUDEBAKER RD
                     CERRITOS CA 90701

      **************** PRODUCT NAME ****************

    **00019*  TRIFLURALIN EMULSIFIABLE CONCENTRATE


********************************************************************************

   *REGISTRANT*        *NAME AND ADDRESS*

   *  011603         AGAN CHEM MFGRS., LTD.
                     ASHDOD C/O SOLCOOR INC.
                     415 MADISON AVENUE
                     NEW YORK, NY 10017

      **************** PRODUCT NAME ****************

    **00013*  TRIFLUREX TECHNICAL

    **00014*  TRIFLUREX EMULSIFIABLE CONCENTRATE


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   *REGISTRANT*        *NAME AND ADDRESS*

   *  013801         REGISTRATION CONSULTING ASSOC.
                     C/O CHARLES C. YEAGER
                     9 WEST KNOLL ROAD
                     ANDOVER, MA 01810

      **************** PRODUCT NAME ****************

    **00012*  TRIFLURALIN TECHNICAL
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                    **** PRODUCT SEARCH LISTING ****                PAGE.     11

  1/10/79           FEDERALLY REGISTERED PRODUCTS CONTAINING TRIFLURALIN


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   *REGISTRANT*       *NAME AND ADDRESS*

   *  033660        I PI CI S P A
                    VIA FRATTELLI BELTRAMI 11
                    NOVATE MILANESE, ITALY 00000

      **************** PRODUCT NAME ****************

    **00003*  TRIFLURALIN TECHNICAL
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                    **** PRODUCT SEARCH LISTING ****                 PAGE        1

01/10/79      APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  001471         ELANCO PRODUCTS DIVISION ELI LILLY
                     ATTN: RALPH HILL                             3172612535
                     PO BOX 1750
                     INDIANAPOLIS IN 46206

      **************** PRODUCT NAME ****************

    **04575*  TREFLAN E.C.

    **04576*  TREFLAN E.C.

    **04577*  TREFLAN E.C.

    **04626*  TREFLAN E.C.

    **04627*  TREFLAN E.C.

    **04628*  TREFLAN E.C.

    **04639*  TREFLAN E.C.

    **04640*  TREFLAN E.C.

    **04641*  TREFLAN E.C.

    **04642*  TREFLAN E.C.

    **04643*  TREFLAN E.C.

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   *REGISTRANT*        *NAME AND ADDRESS*

   *  002935         WILBUR ELLIS CO.
                     191 W. SHAW AVE SUITE 107
                     FRESNO, CA 93704

      **************** PRODUCT NAME ****************

    **06591*  GREEN PRIDE 3 IN 1 ROSE CARE
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01/10/79      APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING TRIFLURALIN

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  *REGISTRANT*        *NAME AND ADDRESS*

  * 005735          TIDE PRODUCTS INC.
                    ATTN: M.W. MARSH                          5123834901
                    BOX 1020
                    EDINBURG, TEXAS 78539

    **************** PRODUCT NAME ****************

   **04816*  TIDE WEED & FEED WITH TREFLAN

   **04818*  TIDE WEED & FEED FOR COTTON-FALL APPLICATION

   **04835*  TIDE WEED & FEED FOR SOYBEANS

   **04836*  TIDE WEED & FEED FOR SOYBEANS

   **04840*  TIDE WEED & FEED FOR SOYBEANS(CONTAINS .2% TREFLAN &1.0 VERNAM)

   **04841*  TIDE WEED & FEED FOR SOYBEANS

   **04843*  TIDE WEED & FEED COTTON & SOYBEANS

   **04844*  TIDE WEED & FEED FOR COTTON & SOYBEANS

   **05530*  TIDE WEED & FEED WITH TREFLAN (CONTAINS .2% TREFLAN)

   **05531*  TIDE WEED & FEED WITH TREFLAN (CONTAINS .3% TREFLAN)

   **05535*  TIDE WEED & FEED FOR SOYBEANS


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  *REGISTRANT*        *NAME AND ADDRESS*

  * 008278          METRO BIOLOGICAL LAB
                    8241 GAY ST
                    CYPRESS CA 90639

    **************** PRODUCT NAME ****************

   **09246*  METRO (TESTED) CURE IT
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01/10/79      APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING TRIFLURALIN

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  010163        GOWAN COMPANY
                   P. O. BOX 5696
                   YUMA, ARIZONA 85364

     **************** PRODUCT NAME ****************

   **06401*  PROKIL TRIFLURALIN 4 EC (EPA FILE SYMBOL 10163-TE)

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  010583        GENERAL CONTROL COMPANY INC
                   2126 S ALVERNON
                   TUCSON AZ 85711

     **************** PRODUCT NAME ****************

   **03260*  CONTROL-RAPID KILL#1

   **08653*  CONTROL-RAPID KILL#1

   **09353*  CONTROL-RAPID KILL #1

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  *REGISTRANT*        *NAME AND ADDRESS*

  *  011093        MASTER NURSERYMEN'S ASSN C/O LEO DUPUICH
                   3620 1/2 MT DIABLO BLVD
                   LAFAYETTE CA 94549

     **************** PRODUCT NAME ****************

   **07125*  49'ER GOLD STRIKE BRAND GRANULAR GARDEN WEEDER
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                    **** PRODUCT SEARCH LISTING ****
                                                             PAGE      8
 01/10/79      APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING TRIFLURALIN

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    *REGISTRANT*        *NAME AND ADDRESS*

    *  037800           BURDETTE MILL & GIN, INC.
                        BOX 278
                        WASHINGTON, GA 30673

       **************** PRODUCT NAME ****************

    **08386*  FERTILIZER CONTAINING

    **08387*  FERTILIZER CONTAINING

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    *REGISTRANT*        *NAME AND ADDRESS*

    *  037820           KINDER CANAL CO., INC.
                        BOX 338
                        KINDER, LA 70648

       **************** PRODUCT NAME ****************

    **08426*  TREFLAN EC

    **08432*  SENCOR-TREFLAN EC

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    *REGISTRANT*        *NAME AND ADDRESS*

    *  037821           LANEHART LIQUID FERT. CO.
                        BOX 141
                        KEO, AR 72083

       **************** PRODUCT NAME ****************

    **08429*  LANEHART BRAND 5-15-20 FERTILIZER WITH .4% TREFLAN
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                    **** PRODUCT SEARCH LISTING ****                    PAGE

  01/10/79     APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*         *NAME AND ADDRESS*

   *  037847          RICELAND SEED CO.
                      303 N. MAIN BOX 32
                      STUTTGART, AR 72160

     **************** PRODUCT NAME ****************

    **08315*  RISCO-4-12-24 WITH TREFLAN

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   *REGISTRANT*         *NAME AND ADDRESS*

   *  037863          BOGARD GRAIN & SEED CO., INC.
                      BOX 720
                      STUTTGART, AR 72160

     **************** PRODUCT NAME ****************

    **08155*  TREFLAN

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   *REGISTRANT*         *NAME AND ADDRESS*

   *  037914          SMITH-SHEPPARD CONCRETE CO INC
                      BOX 755
                      SANDERSVILLE, GA 31082

     **************** PRODUCT NAME ****************

    **09223*  TREFLAN E.C.
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                    **** PRODUCT SEARCH LISTING ****                    PAGE

01/10/79       APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING TRIFLURALIN

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   *REGISTRANT*          *NAME AND ADDRESS*

   *  03865[illegible]          N.Y.S. COLLEGE OF AGRIC. AND LIFE SCI. CORNELL UNI
                     ATTENTION: DR. DEWEY
                     ITHACA, NEW YORK 14853                        6072563233

      ***************** PRODUCT NAME ****************

   **10[illegible]43*  NYS-DEWEY-TREFLAN

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   *REGISTRANT*          *NAME AND ADDRESS*

   *  038749         R. F. LINDSEY & SONS
                     ROUTE 2
                     CENTRE, AL 35960

      ***************** PRODUCT NAME ****************

   **10311*  ELANCO TREFLAN E.C.

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   *REGISTRANT*          *NAME AND ADDRESS*

   *  039863         USDA, APHIS, PPQ
                     ROOM 318, FEDERAL BUILDING
                     RALEIGH, N.C. 27601

      ***************** PRODUCT NAME ****************

   **10[illegible]73*  TREFLAN E.C.
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